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Frequency of behavioral symptoms characterizes agitation in Alzheimer's disease

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SUMMARY

This study describes two well-characterized groups of Alzheimer's disease (AD) patients with similar levels of cognitive functioning, but with different overall behavioral disturbance levels. We sought to determine the nature of this difference – whether AD patients with higher levels of behavioral disturbance (n = 148) differ from less disturbed AD patients (n = 235) in terms of (a) the range of symptoms exhibited, (b) the frequency of occurrence of these symptoms, or (c) both of these. We defined and operationalized 'diversity of behaviors' and 'frequency' with respect to the item-level responses on the Cohen-Mansfield agitation inventory (CMAI). We found that, in these two samples of AD patients, differences occurred in the frequency of 10 out of 21 behaviors, rather than in a variety of endorsed behaviors. These 10 behaviors, observed at different frequencies in both groups, may be useful for monitoring change in studies of drugs or behavioral interventions for behavioral disturbance in persons with AD.

Keywords

Alzheimer's disease; assessment; agitation; behavioral disturbance

INTRODUCTION

Behavioral disturbance in Alzheimer's disease (AD) is common, and is an important aspect of the disease because of its impact on patient management and on quality of life for patients and caregivers (Haupt and Kurtz, 1993; Morris *et al.*, 1996). For these reasons, behavioral disturbance, especially agitation, in persons with AD or other dementing illnesses have been

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the target of recent clinical trials (Mittelman *et al.*, 1996; Sultzer *et al.*, 1997; Devanand *et al.*, 1998; Tariot *et al.*, 1998; Katz *et al.*, 1999; Teri *et al.*, 2000).

A number of assessment instruments have been used to evaluate the effects of specific interventions, such as the Cohen-Mansfield Agitation Inventory (Cohen-Mansfield, 1986, 1991) and the CERAD Behavioral Rating Scale for Dementia (Tariot *et al.*, 1995). Although some instruments measure both the frequency and severity of symptoms (Patterson and Bolger, 1994; Weiner *et al.*, 1996), most elicit only caregiver ratings of the frequency of occurrence. Instruments usually generate a total score, and in some cases subscores describing specific behavioral domains. Changes in total scores and subscores are typical endpoints used to assess the efficacy of the treatment or intervention (e.g., Devanand *et al.*, 1998; Katz *et al.*, 1999).

However, changes in these scores can only reflect the overall level of symptomatology. When two patients, assessed with the same instrument, are found to have different total scores, it is impossible to determine if one person is rated as more disturbed than another because they exhibit a wider range of behaviors than the other, or because they exhibit the same behaviors but with greater frequency. It is also possible that both a wider range and a greater frequency explain the observed difference. Thus, although comparing total scores may differentiate two individuals, the basis of this differentiation will be in terms of the general, and not the specific, disturbance.

Alternatively, two assessments might yield similar total scores. When two patients, assessed with the same instrument, have similar total scores, it is impossible to determine whether qualitative differences in the manifestation of agitation across the two individuals are obscured; symptoms could be fewer in number but greater in frequency in one, while greater in number but with very low frequency in the other. In this case, the two individuals could be characterized as similar, when in fact, their symptomatologies could be very different. Different interventions might be warranted for an individual with a few, very frequent and very disturbing symptoms than would be warranted for an individual with several infrequent and not particularly disturbing symptoms; however, with similar total scores, the practicality of utilizing different approaches is obscured.

Both of these situations could also occur when the same patient is rated twice with the same instrument; and comparison of the total scores and subscores over time will not pinpoint specific differences which might provide important information about the patient’s progression or response to the intervention. This is especially important in clinical trials for interventions for behavioral symptoms in persons with AD. Therefore, to effectively investigate treatments for agitation in AD, item-level differences which underlie overall levels of disturbance must be better understood.

In this study we sought to understand the item-level differences between two independent groups of AD patients with similar levels of cognitive functioning, but different levels of overall behavioral symptomatology (agitation), as assessed by the Cohen-Mansfield agitation inventory (CMAI) total score (Cohen-Mansfield, 1991; and see Koss *et al.*, 1997 for AD-specific CMAI administration). Subjects were participants in one of two clinical

trials, described below, carried out by the Alzheimer's Disease Cooperative Study (ADCS) (Thal, 1997). We analyzed responses to the individual CMAI items taken from the baseline visit in each study. To determine if the differences in total CMAI scores were due to differences in the frequency or in the diversity of behaviors observed, or to both, we compared the frequency ratings per item across the groups, as well as those symptoms which were observed in a specified proportion of both groups.

METHODS

The data in this study were collected from community-dwelling AD patients enrolled in two separate ADCS-conducted, National Institute on Aging sponsored multi-center studies. The instrument protocol (IP) was designed to evaluate an array of assessment instruments, including the CMAI, for AD patients with varying levels of dementia. The agitation protocol (AP) was a randomized, controlled clinical trial of therapies for agitated behaviors. Informed consent was obtained for all participants from their caregivers. Cognitive status for both protocols was assessed in a screening visit with the Mini-Mental State Examination (MMSE) (Folstein *et al.,* 1976). Behavioral assessments were made at the baseline visit and prior to any systematic therapeutic intervention in the latter group. Exclusion criteria for both studies included a recent (two-year) history of major psychiatric disorders, including depression.

Subjects

Evaluation of Instruments Protocol group (IP)—Subjects were 242 community-dwelling persons with National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)-based diagnosis of probable AD (McKhann *et al.,* 1984) recruited to a multi-site study of the reliability and validity of a battery of assessment instruments for research in AD (Ferris *et al.,* 1997). Of these 242, seven had also participated in the Agitation Protocol; their responses were excluded from the IP group and included in the AP group, reducing the number of subjects in the IP group to 235. Eligibility for the IP study required the discontinuation of psychoactive medication, including but not limited to antidepressants, neuroleptics and anxiolytics, for four weeks prior to the baseline visit, except for patients with MMSE < 10, who could continue on drugs (n = 11).

Agitation Protocol group (AP)—Subjects were 148 community-dwelling persons with NINCDS-ADRDA-based diagnosis of probable AD recruited to a multi-site study of treatments for agitation in AD (Teri *et al.,* 2000). All had at least a two-week history of two or more agitated behaviors on the Agitated Behaviors in Dementia scale (ABID) (Logsdon *et al.,* 1999) at the screening visit. Two weeks prior to the baseline visit, participants were required to discontinue all antipsychotics, antidepressants, anxiolytics, stimulants, anti-convulsants, anti-manics, narcotic analgesics, anti-Parkinson agents, sedating antihistamines, beta-blockers, phenothiazine anti-nausea drugs, sedative/hypnotics, and oral gluco-corticoids. Subjects who could not discontinue these drugs were not eligible for this trial.

Comorbid psychiatric conditions were exclusionary criteria in both studies.

Materials

The CMAI has been described in detail elsewhere (Weiner *et al.,* 1996; Koss *et al.,* 1997). The version used in these studies includes 38 items, 36 of which describe specific behaviors[1] and are investigated here. Caregivers rated the frequencies at which these 36 items were observed in the AD patient during the preceding two weeks along a seven-point scale. The range of responses runs from 'never occurred' = 0 to 'several times an hour' = 6.[2]

Design and procedure

The data collection from each study has been described in detail elsewhere (Teri *et al.,* 2000; Ferris *et al.,* 1997). The individual CMAI-item responses from the baseline visit for AD patients in each group were compared as indicated below. To determine if diversity, frequency, or both, were factors in the difference in overall behavioral disturbance between these two AD groups, we defined these two characteristics and tested them for each CMAI item per group. We also compared the groups on their total CMAI scores, MMSE scores, and on several demographic variables.

Operational definitions and statistical methods

For our investigation of the diversity of behaviors observed in each group, we sought to identify those items which were endorsed in each group. Once the set of endorsed items was identified in each AD group, we compared the behaviors comprising the sets. Significant differences in the sets of items endorsed would be interpreted as representing 'diversity' of behaviors as differentiating the two groups.

Cohen-Mansfield *et al.* (1995) omitted from their analyses any item endorsed by 5% or fewer subjects in the sample. In the present study, to compare the diversity of symptoms exhibited in each group, we formalized this 'at least 5% endorsement' rule by conducting *t*-tests with the cut-off value of 0.10. We compared the means of the frequency ratings per item in each group to this cut-off mean frequency value. If more than 5% of individuals in a group had a frequency rating of at least once in the past two weeks on an item, then the group mean frequency would be greater than this cut-off value (0.10), and these items were characterized as 'endorsed' by that group. Conversely, if the mean frequency rating for an item was lower than 0.10, then it must have been rated as at least once in the previous two weeks in fewer than 5% of the subjects, and was thus 'unendorsed' by that group. Items endorsed in one group and not the other would represent a difference across the two groups in the range, or diversity, of symptoms exhibited.

CMAI-item ratings were used to explore differences in frequency across the groups as described below. 'Frequency' was defined as the mean item rating per group. Significant differences in frequency across the two groups would be interpreted as representing a role for this factor in differentiating the two AD groups.

[1]The items not considered were 'other behaviors' and 'time of day when behaviors occurred'.
[2]The prescribed scoring ranges from 1 to 7, with 0 representing NA; however, our scoring is to call NA 'missing' and rate frequency from 0 to 6. See Koss *et al.* (1997).

All statistical analyses were carried out with SPSS 8.0 and SPLUS 4.5 for Windows 98. Chi-square tests were conducted on all categorical background variables. *t*-tests were used to determine endorsement, i.e., whether the mean frequency rating for an item was significantly more than our cut-off of 0.10. Items failing to reach significance on these *t*-tests were labeled 'unendorsed' by the group; lists of unendorsed items were compared across groups to determine if there were behaviors observed in one group and not in the other (diversity). Mann–Whitney tests were conducted to compare the populations on total scores, as well as continuous demographic variables, and to compare the groups on frequency ratings for each item (frequency).

All *p*-values were adjusted according to Holm (1979) in order to account for multiple comparisons, and adjusted *p*-values < 0.05 were considered significant.

RESULTS

Demographics/cognitive status

The demographic data are presented in Table 1.

The two groups did not differ on cognitive status as measured by the MMSE at screening ($z = -0.54$, $p = 0.60$), years of education ($z = -1.4$, $p = 0.17$), gender (Chi-square (1) = 1.4, $p = 0.24$), or ethnicity (Chi-square (4) = 8.5, $p = 0.074$). As expected, CMAI total scores were significantly higher for AP ($z = -5.6$, $p < 0.01$). Age was slightly, but significantly, higher in the AP group ($z = -2.6$, $p < 0.05$).

Item analysis

Our item analyses examined both the endorsement of each item per group and the average frequency rating of each item per group. We found that 14 of 36 items were unendorsed in both groups: spitting; verbal sexual advances; physical sexual advances/exposure; grabbing or snatching things from others; hitting; kicking; tearing/destroying objects/property; pushing other people; biting; scratching; hurting self with harmful object; hurting others with harmful object; appearing to fall intentionally; and eating/drinking non-food substances (items 10, 12, 13, 20, 25, 26, 28, 30, 31, 32, 33, 34, 35 and 36). One other symptom, throwing/knocking things (item 27), qualified as 'endorsed' by AP and as 'unendorsed' by IP. The mean frequency ratings of these 15 items did not differ across the groups (see Table 2).

Table 2 contains the means and standard deviations for item frequency ratings, as well as the proportion endorsing each of the 36 behavioral items on the CMAI, for each group. Analyses showed that, while all items except for 2 and 26 (relevant interruptions, kicking) had higher average frequency ratings in AP than in IP, when adjustments were made for multiple comparisons, only the differences in ratings for 10 of the 36 items reached significance: screaming, shouting or howling; making unwarranted requests for attention or help; being negative or uncooperative; cursing, verbally threatening or insulting; verbally bossy or pushy; restlessness or fidgetiness; pacing or wandering; hoarding or collecting; hiding objects; and verbal or non-verbal expressions of anger (items 5, 7, 8, 9, 11, 14, 15, 21, 22 and 24). These are indicated by an asterisk in Table 2.

The majority of caregivers (> 50%) in both groups rated most items as not having occurred (0) or as having occurred less than once a week in the preceding two weeks (1). The exceptions were two items: repetitiveness and restlessness (items 1 and 14), which the majority of both groups rated as occurring at least once or twice a week. Additionally, there were five items which occurred at least once or twice a week in the majority of the AP group, and in the minority of the IP group: complaining; uncooperativeness; pacing; inappropriate handling of objects; and expressions of anger (items 6, 8, 15, 19 and 24).

DISCUSSION

We found no difference in the proportions of caregivers reporting 'other' behaviors on the CMAI (AP: 11.5%, IP: 10.3%). This suggests that the majority of the agitated behaviors that differentiate these more and less behaviorally-disturbed AD patients are contained in the CMAI. However, this study was limited by the scope of the instrument, in that emotional states and disturbed ideation were not assessed. The groups were found not to differ in terms of the average severity of AD (MMSE scores) or educational levels, so association of either of these variables with CMAI total score or item endorsement was not considered a factor in our results.

Physically aggressive behaviors were rarely endorsed, and were not exhibited differentially across the two populations. This may be a result of the recruiting requirements of the two studies from which the subjects were drawn, i.e., that they be living in the community rather than in extended care facilities.

Further, the baseline agitation levels in the AP group were assessed after two- or four-week drug washout, which may have inflated the degree of agitation observed. Conversely, study requirements included that all participants be able to discontinue psychoactive drugs for two weeks or one month prior to the study; behaviorally disturbed AD patients who were not able to discontinue these medications were ineligible. Therefore, these subjects may be considered typical of *un*medicated outpatients with AD.

CONCLUSIONS

We found that two groups of AD patients with differing levels of overall behavioral disturbance, but similar overall cognitive function, could be discriminated based on the frequency of their behaviors, rather than on the diversity of the behaviors they exhibited. We found that the range of symptoms was essentially the same for 35 of the 36 symptoms in these two groups.

We also found that only 10 of the 21 symptoms, which were exhibited in both groups, were significantly more frequent in the more agitated than the less agitated group. Therefore, while the 21 observed items may represent the most common symptoms of agitation in persons with AD, these 10 items (screaming, shouting or howling; making unwarranted requests for attention or help; being negative or uncooperative; cursing, verbally threatening or insulting; verbally bossy or pushy; restlessness or fidgetiness; pacing or wandering; hoarding or collecting; hiding objects; and verbal or non-verbal expressions of anger) are symptoms which may be likely to occur differentially across individuals. These 10

symptoms, when occurring together with relatively high frequency, may represent an 'agitation syndrome' in persons with AD, characterized by inappropriate verbal and motoric behaviors, whereas the low-level presence of the 21 symptoms observed in both groups may be indicative of a more general behavioral change associated with AD.

The 10 symptoms listed above may represent a core of behavioral disturbance in AD, and therefore may be the most appropriate to monitor in clinical studies. They may also be considered indicators of higher levels of agitation for community-dwelling AD patients when recruiting or grouping subjects according to 'higher' or 'lower' levels of disturbance (e.g., for clinical trial eligibility criteria). Another implication of these results is that changes in frequency of particular behaviors may be more effective parameters for assessing treatment efficacy for persons with AD than changes in the total behavioral score. We agree with Cummings (2000) that targeted symptom reduction, as opposed to a general reduction in agitated or disturbed behaviors, as indicated by change in total score, may be a more reasonable and attainable treatment goal, and may also have greater heuristic value. That is, the general behavioral changes associated with AD may be secondary to depressive symptoms (e.g., trying to hurt self), decreasing functional levels (e.g., grabbing and snatching), or confusion (e.g., trying to get out). Treating the agitated symptoms in these cases might not be as effective as treating the more primary symptoms (in these examples, depressive symptoms, environmental demands or unfamiliarity in the environment). A more specific 'agitation syndrome' may be more sensitive to targeted symptom reduction by pharmacologic intervention or a combination with both pharmacologic and non-pharmacologic approaches.

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Table 1

Demographics of two AD populations

Baseline characteristics	Instrument protocol (IP)	Agitation protocol (AP)
Age†	72.3 ± 9.0	74.8 ± 7.1
Education (years)	13.2 ± 2.9	12.6±3.5
MMSE	12.8 ± 7.9	13.2 ± 7.5
Gender breakdown	61% women	55% women
Ethnicity	85.5% white, 10.8% black*	92.3% white, 5.5% black**
CMAI total score‡	27.1 ± 20.6	39.2 ± 22.7

MMSE, Mini-Mental State Exam; CMAI, Cohen-Mansfield Agitation Inventory.

* < 5% Hispanic or Native American;

** < 5% Hispanic or Asian.

† $p < 0.05$;

‡ $p < 0.01$.

Table 2

Frequency ratings (mean (SD)) (range: 0–6); group endorsement percentages for CMAI items

CMAI item	IP (*n* = 235)	AP (*n* = 148)
1. Was repetitive	3.48 (2.15)‡; 77%†	3.79 (2.08); 81.8%
2. Relevant verbal interruptions	1.00 (1.55); 27.8	0.76 (1.26); 23.7
3. Irrelevant verbal interruptions	1.47 (1.92); 36.8	1.69 (1.91); 46.6
4. Making strange noises, including laughter/crying	0.93 (1.79); 21.9	1.07 (1.75); 28.4
5. * Scream, shout or howl	0.39 (1.09); 11.6	0.80 (1.46); 23.0
6. Complain or whine	1.52 (1.88); 39.2	2.18 (2.09); 56.1
7. * Unwarranted requests for attention or help	0.91 (1.66); 21.9	1.69 (2.12); 39.2
8. * Was negative, uncooperative, unwilling	1.38 (1.61); 41.0	2.20 (1.95); 60.5
9. * Curse or verbally threatening/insulting	0.69 (1.26); 20.8	1.36 (1.73); 38.5
10. Spitting	0.20 (0.87); 5.2	0.30 (1.05); 8.1
11. * Verbally bossy or pushy	0.63 (1.29); 17.7	1.28 (1.88); 33.8
12. Verbal sexual advances	0.20 (0.68); 6.5	0.52 (1.50); 8.4
13. Physical sexual advances/exposure	0.19 (0.76); 5.6	0.22 (0.85); 5.4
14. * Restless or fidgety	2.57 (2.32); 58.4	3.74 (2.20); 77.7
15. * Pace or wander aimlessly	2.05 (2.35); 45.1	3.02 (2.41); 65.3
16. Try to get out, sneak out, or enter other places	0.48 (1.17); 13.7	0.60 (1.32); 16.9
17. Dress or undress inappropriately	0.53 (1.28); 14.8	0.79 (1.38); 25.0
18. Repetitious mannerisms	1.60 (2.20); 36.9	2.03 (2.43); 41.9
19. Handle things inappropriately	1.79 (2.09); 43.4	2.43 (2.12); 60.5
20. Grab or snatch things from others	0.17 (0.64); 4.7	0.28 (0.90); 7.4
21. * Hoard or collect objects	1.14 (1.84); 27.9	1.79 (2.09); 44.2
22. * Hide objects	1.09 (1.76); 27.5	1.98 (2.08); 49.3
23. Strange movements	0.42 (1.29); 9.4	0.64 (1.59); 15.7
24. * Temper outburst/verbal, non-verbal expressions of anger	1.07 (1.38); 34.3	1.93 (1.74); 54.1
25. Hit people, self or objects	0.22 (0.78); 6.4	0.28 (0.89); 8.1
26. Kick people or objects	0.10 (0.54); 2.6	0.08 (0.40); 2.7
27. Throw things or knock objects off surfaces	0.18 (0.68); 5.2	0.33 (0.91); 8.1
28. Tear or destroy objects/property	0.16 (0.65); 3.9	0.26 (0.96); 5.4
29. Grab onto or cling to people	0.53 (1.40); 12.9	0.92 (1.78); 21.1
30. Push other people	0.07 (0.33); 2.2	0.29 (0.89); 8.8
31. Bite people or things	0.02 (0.17); 0.43	0.03 (0.25); 1.4
32. Scratch people, self or things	0.07 (0.53); 1.7	0.27 (1.07); 6.1
33. Hurt self with harmful object	0.00 (0.07); 0.0	0.02 (0.14); 0.0
34. Hurt others with harmful object	0.00 (0.07); 0.0	0.01 (0.08); 0.0
35. Appear to fall intentionally	0.00 (0.07); 0.0	0.05 (0.58); 0.0
36. Eat/drink non-food substances	0.08 (0.41); 1.7	0.16 (0.77); 3.4

CMAI, Cohen-Mansfield Agitation Inventory; IP, instrument protocol; AP, agitation Protocol.

[*] Holm-adjusted p-values < 0.05 for Mann–Whitney tests comparing frequency ratings.

[†] % of group endorsing the item;

[‡] Mean (SD) frequency rating.