Selected Psychiatric Symptoms Associated With Rate of Cognitive Decline in Patients With Alzheimer's Disease

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Abstract

We examined the relation between selected psychiatric symptoms and the average rate of decline in different areas of cognition in patients with Alzheimer's disease. Measures of decline were computed by determining patients' average rates of decline on the underlying factors of the Mini-Mental State Examination (MMSE). Patients with agitation or wandering declined more rapidly on the total MMSE score than did patients without either symptom. The Following Commands factor accounted for almost all of this decline. The findings suggest a relation between the presence of certain behavioral problems in Alzheimer's disease and decline in particular cognitive areas. (*J Geriatr Psychiatry Neurol* 1993;6:235–238).

Alzheimer's disease (AD) gives rise not only to its characteristic decline in cognitive functioning, but to behavioral manifestations, or psychiatric symptoms, as well. These symptoms have a high prevalence in AD; some researchers have placed the estimate at over 50%.[1–3] Psychiatric symptoms achieve special importance in the study of AD because they can affect a patient's general level of functioning and the quality of life of a caregiver.

A broad spectrum of psychiatric problems has been associated with AD, including depression, apathy, anxiety, agitation, obsessive rituals, hypochondriasis, hyperactivity, and combativeness. Furthermore, several researchers have reported an association between the presence of psychiatric symptoms and cognitive status. For example, in a cross-sectional study involving 680 patients, Cooper et al[4] found that several psychiatric symptoms were found to be associated with lower total Mini-Mental State Examination[5] (MMSE) scores. Teri et al[6] conducted a longitudinal study using the total MMSE score as an index of cognitive status and found that problems with awareness and agitation were associated with an increased rate of decline. Although patients who exhibited wandering behavior tended to decline more rapidly than those who did not, the difference was only marginally significant. However, as Teri et al pointed out, their conclusions were limited by the fact that only a small proportion of their subjects exhibited some of the symptoms of interest.

Thus, previous studies of the relation between the presence of psychiatric symptoms and cognitive status have used composite MMSE scores as the cognitive index. Although this approach has provided valuable information, one problem is that the MMSE composite score provides only a general estimate of cognitive status.[6] In the present paper, we elaborate on previous studies[4,6] by examining decline on the underlying factors of the MMSE. The factors that underlie performance on the MMSE when used lon-

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gitudinally were proposed by Tinklenberg et al[7] through factor analysis and are provided in Table 1. The advantage of examining the average rates of decline on the factors of the MMSE is that it allows a somewhat finer-grained look at the pattern of decline. For example, although it is possible that the presence of certain psychiatric symptoms is associated with an increased rate of decline of abilities *in general*, it seems more likely that their presence is associated with decline *in particular areas*. Thus, if the presence of a symptom such as wandering is associated with decline on one factor but not another, then future research can be targeted more specifically.

In the present paper, we adopted a longitudinal approach and examined the average rate of decline on the MMSE, as did Teri et al.[6] We attempted to replicate the pattern of decline that Teri et al reported for composite MMSE scores and explored whether the presence of psychiatric symptoms was associated with more rapid decline in some cognitive areas than in others.

Method

Patients

The 74 patients who participated in this study were part of a longitudinal study conducted at the Stanford National Institute of Mental Health Clinical Research Center for the Study of Senile Dementia. Sixty-five met the National Institute of Neurological and Communicative Disorders and Stroke criteria for "probable" AD,[8] and nine had a "definite" diagnosis confirmed by autopsy. There were 44 men and 30 women; their ages at estimated onset ranged from 47 to 81 years, with a mean of 63.96 years (SD = 8.48 years). No patients were taking any psychotherapeutic drugs at the time of entry into the study.

Assessment of Psychiatric Symptoms

Patients were evaluated for the presence of psychiatric symptoms by trained clinicians, either psychiatrists or research nurse specialists. The presence of delusions, hallucinations, emotional lability, agitation, anxiety, depression, and wandering were coded on the California State Department of Health Services AD Diagnostic and Treatment Center form. The definitions for the State form were based on *DSM-III* definitions.

Mini-Mental State Examination

The MMSE was administered approximately every 6 months. The MMSE is scored on a scale of 0 to 30, and a score of less than 24 is generally regarded as evidence of organic mental disturbance.[5] The first administration was given during initial screening. Patients had from three to six administrations of the test, depending on their length of participation in the study. The mean initial MMSE score for the patients was 18.35 (SD = 7.04).

Computation of Factor Scores

The MMSE factor scores were computed following the procedure of Tinklenberg et al.[7] The scores for each item of the MMSE were first transformed to proportions by dividing the actual score by the maximum possible score for the item; thus, scores for all items were on the same 0-to-1 scale. The average rates of change on the MMSE items were computed separately for each patient by regressing the MMSE scores on time (in years) since the first measurement. The regression coefficient provides an index of the average yearly rate of decline. Factor scores were computed for each patient by taking the mean of the average rates of change of the appropriate items, as proposed by Tinklenberg et al. Because the MMSE scores were transformed to proportions and time was in years, a factor score can be interpreted as the average percent decline per year on a factor

TABLE 1
Proposed Longitudinal Factor Structure of the MMSE

Orientation	Following Commands	Language Repetition	Language Expression	Recall
Orientation (time)	Follow three-stage verbal command	Repeat three unrelated objects	Name a watch and pencil	Recall three objects
Orientation (place)	Read and obey a command	Repeat "no ifs, ands, or buts"	Write a spontaneous sentence	
Serial 7s subtraction				
Copy two polygons				

relative to the factor's maximum score. For example, if a patient's factor score is −0.14, then the patient declined an average of 14% of the maximum score per year on that factor.

Results

Of the 74 patients, the proportion with psychiatric symptoms ranged from 22% for emotional lability to 76% for anxiety, as shown in Table 2. The average rates of decline for patients with and without the symptoms are provided in Table 3. Two symptoms were associated with a faster rate of decline on total MMSE scores: agitation and wandering. The Following Commands factor was the only MMSE factor that declined significantly faster in patients with agitation and wandering than in patients without these symptoms; in other words, most of the total MMSE decline could be accounted for by decline on this factor alone (Table 4). Although there were no significant differences in the rates of decline between patients with and without the other five symptoms, in each case the trend was for faster decline in patients with the specific symptom. There were no significant differences in age at onset and initial MMSE scores between patients with and without symptoms, except that subjects reporting hallucinations had a slightly earlier age at onset (61.5 years) than did patients without hallucinations (65.8 years) ($t[72] = 2.19$; $P < .05$).

Discussion

Our findings indicate that the presence of agitation or wandering is associated with accelerated decline in overall cognitive function as measured by the MMSE. We replicated the finding of Teri et al[6] of more rapid decline in patients who exhibited agitation and also found more rapid decline in patients who exhibited wandering behavior. Moreover, we were able to elaborate on these findings in that rapid decline appeared to be almost wholly due to decline on the Following Commands factor of the MMSE.

One interpretation of our findings is that the inability to follow commands leads to frustration and is thus expressed as inappropriate motor behavior and agitation. Alternatively, it may be that the inability to follow simple commands as measured by the MMSE reflects a broader inability to follow instructions of caregivers or nursing facility staffs. It is not difficult to see how this inability could lead to conflict and be interpreted as "agitation." In fact, caregivers have noted that agitation and aggression are often elicited when certain AD patients are told by the caregiver to do something.[9]

Additional studies of the association between

TABLE 2
Frequencies of Symptoms

Symptom	Absent, n (%)	P
Delusions	32 (43)	42 (57)
Hallucinations	42 (57)	32 (43)
Emotional lability	58 (78)	16 (22)
Agitation	27 (36)	47 (64)
Anxiety	18 (24)	56 (76)
Depression	40 (54)	34 (46)
Wandering	39 (53)	35 (47)

TABLE 3
Average Rate of Decline on MMSE Composite Score for Patients With and Without Symptoms

	Average Rate of Decline			
Symptom	Absent	Present	$t(72)$	P
Delusions	−.10 (.08)	−.12 (.07)	1.17	.244
Hallucinations	−.10 (.07)	−.12 (.07)	1.02	.313
Emotional lability	−.11 (.08)	−.12 (.05)	0.66	.511
Agitation	−.09 (.09)	−.13 (.06)	2.30	.025
Anxiety	−.10 (.08)	−.12 (.07)	0.62	.539
Depression	−.10 (.07)	−.12 (.07)	1.11	.269
Wandering	−.09 (.08)	−.13 (.05)	2.59	.013

*Mean (SD).

TABLE 4
Comparison of the Average Rates of Change of the Five MMSE Factor Scores and Total MMSE Score in Patients With or Without Agitation or Wandering

	Orientation	Following Commands	Language Repetition	Language Expression	Recall	Total MMSE
Agitation						
Absent (n = 27)	−0.10(0.13)*	−0.11(0.13)	−0.11(0.15)	−0.12(0.15)	0.00(0.20)	−0.09(0.09)
Present (n = 47)	−0.12(0.09)	−0.22(0.14)	−0.11(0.12)	−0.14(0.10)	−0.05(0.06)	−0.13(0.06)
t (72)	0.63	3.28	0.72	0.67	1.67	2.29
P	.528	.002	.943	.502	.099	.024
Wandering						
Absent (n = 39)	−0.10(0.12)	−0.14(0.13)	−0.10(0.14)	−0.10(0.12)	−0.02(0.15)	−0.09(0.08)
Present (n = 35)	−0.12(0.08)	−0.23(0.15)	−0.12(0.11)	−0.15(0.12)	−0.04(0.10)	−0.13(0.05)
t (72)	0.74	2.81	0.93	1.78	0.82	2.56
P	.463	.006	.353	.080	.413	.013

*Mean (SD).

more rapid decline in ability to follow commands and wandering or agitation could lead to more accurate knowledge of abnormal behaviors and, ultimately, better placement decisions. Should cognitive measures prove useful in this regard, the resulting information would be relevant for patients whose rapid course and young age might not allow adequate warning of the need for institutionalization.[10] Future research should attempt to hone both our understanding of the cognitive factors involved in such behavior and cognitive testing procedures.

Finally, these results underscore the need for cognitive/behavioral interventions and innovative medications to manage disruptive behavior in AD. Because the presence of psychiatric symptoms such as psychosis and anxiety were not associated with the rate of decline on the Following Commands factor, they may not be critical elements in the pathway to agitation. In fact, antipsychotic and antianxiety drugs are not consistently successful in treating acute agitation of AD.[11] Anticholinergic side effects of antipsychotic medications and the impairment of short-term memory caused by benzodiazepines can both contribute to confusion in demented patients.[12] Better understanding of cognitive mechanisms related to disruptive behavior may allow more rational pharmacologic therapy of such behavior in the future.

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