

Longitudinal Assessment of Patient Dependence in Alzheimer Disease

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Background: The Dependence Scale measures the amount of assistance patients with dementia require in performing daily activities. Validity and reliability of this scale have been demonstrated, but the progression throughout long periods in patients with Alzheimer disease (AD) has not previously been examined.

Objective: To determine the longitudinal course of patient dependence in a cohort of prospectively followed AD patients.

Methods: Two hundred thirty AD patients enrolled in the Predictors Study were followed up prospectively at 6-month intervals for an average of 6.5 visits. The Dependence Scale was administered to a caregiver, and patients were assessed with the modified Mini-Mental State Examination (mMMSE) and the Blessed Dementia Rating Scale. Dependence level and the additive sum of the Dependence Scale items were considered for analysis.

Results: Generalized estimating equations to regression analyses were used to determine that both Dependence Scale scores and dependence level significantly decline with time. By covarying mMMSE scores and self-care deficits factor scores of the Blessed Dementia Rating Scale, generalized estimating equations analysis also demonstrated that change in patient dependence was independent of global cognitive decline and other measures of activities of daily living, respectively.

Conclusions: This study shows the validity of the Dependence Scale and demonstrated that dependency in AD significantly declines with time independent of global cognition and other self-care deficits. The scale is a valuable instrument for outcomes research, efficacy trials, and behavioral research in AD.

Arch Neurol. 2002;59:1304-1308

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FUNCTIONAL DISABILITY is a defining feature of Alzheimer disease (AD).¹ However, functional impairment is not a uniform construct but is multifaceted and can be measured with various clinical instruments. For example, traditional scales have focused on self-care needs and instrumental activities of daily living.^{2,3} Others consider patient disability⁴ and caregiver burden.^{5,6} The Dependence Scale⁷ was developed to assess the required amount of assistance needed by AD patients to better understand the impact of the disease on patients and their caregivers.

Since its introduction, the Dependence Scale has been included in several efficacy trials for new treatments of AD,⁸⁻¹⁰ behavioral studies,¹¹⁻¹⁶ and position papers.¹⁷⁻²² Overall, the scale has been a useful tool for characterizing functional impairment and for examining efficacy of treatment. It has been suggested that the Dependence Scale also has utility for ex-

amination of the functional course of AD from mild to the most advanced stages of the disease.¹⁸

In the initial validity and reliability study, Stern et al⁷ demonstrated good agreement with measures of cognitive impairment and other functional impairment scales. They further showed that the scale is organized hierarchically, tapping into dependency needs affected both early and late in the disease. A subset of patients enrolled in that original study were followed up longitudinally and tested at 6-month intervals for approximately 18 months. Preliminary longitudinal analysis demonstrated excellent test-retest reliability and provided evidence that dependency needs increase with time.

In the current study, AD patients enrolled in the Predictors Study were followed up longitudinally at 6-month intervals for up to 10 years. Patients were assessed with the Dependence Scale at each visit. The primary purpose of the study was to characterize the course of patient de-

PARTICIPANTS AND METHODS

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Participants (n=230) were informants who represented patients in the Predictors Study, which prospectively examines the course of AD. Patients were recruited from Columbia University (n=92), Johns Hopkins University (n=77), and Massachusetts General Hospital (n=61). To be entered into this study, patients were required to meet National Institute of Neurological and Communicative Disorders and Stroke diagnostic criteria for probable AD¹ and to demonstrate relatively mild cognitive impairment, as indicated by a score of 30 or greater on the modified Mini-Mental State Examination (mMMSE). Additional detailed description of inclusion and exclusion criteria for the Predictors Study are described elsewhere.^{23,24}

PROCEDURES

As part of the Predictors Study, AD patients are assessed prospectively every 6 months with a standard battery of clinical and neuropsychological tests. The Dependence Scale is administered to a reliable informant at each visit. The scale consists of 13 items, representing a range of severity from mild (eg, "Does the patient need frequent help finding misplaced objects?") to moderate (eg, "Does the patient need to be watched when awake?") and severe (eg, "Does the patient have to be fed?") levels of dependency. The scale is designed to ascertain the current level of dependency.

Table 1 gives the entire Dependence Scale. A dependence score is derived by taking an additive sum of the 13 items. Furthermore, a 6-level ranking of dependence is determined as follows: level 0, 0 to all items; level 1, items A, B, or C equals 1; level 2, 2 of items A, B, or C equals 1, or A or B equals 2, or D equals 1; level 3, items E, F, or G equals 1; level 4, items H, I, or J equals 1; level 5, items K, L, or M equals 1. The 6 dependence levels are based on responses to the Dependence Scale items and range from no dependence to complete dependence in self-care activities. Rank levels were created to establish dependency stages and have been used in all studies to date that used the scale.

For the purposes of this study, we used mMMSE scores obtained at each visit to assess global level of cognitive status. The mMMSE is a modification of the Folstein Mini-Mental State Examination²⁵; scores range from a minimum of 0 points to a maximum of 57. Psychometric properties of the scale are described by Stern et al.²⁶

Similarly, the Blessed Dementia Rating Scale (BDRS)²⁷ was conducted at each visit to measure functional capacity. In addition to a total score, a well-defined 4-factor model has previously been described.²⁷ The factors include cognitive impairment, self-care needs, personality disturbance, and apathy.

STATISTICAL ANALYSIS

The sum of the Dependence Scale items was assessed longitudinally with generalized estimating equations (GEEs) to regression analyses with repeated measures.²⁸ There are several advantages to using GEE analysis. It allows for analysis with multiple visits per participant and corrects for the fact that the characteristics of a single individual over time are likely to be correlated with one another. In GEE analysis, repeated measures for each participant are clustered. Furthermore, GEE analysis takes into account the status or changing value of covariates at each visit. Tabled values for regression analyses involving the factor score are regression coefficients and their SEs. The dependent measure for the GEE analysis was the sum of the items on the Dependence Scale. To investigate whether dependency change over time is independent of global cognition, the GEE analysis was rerun with mMMSE score at each visit held as a covariate. Further analysis was performed with the self-care needs factor of the BDRS score held as a covariate. For this analysis, we wished to determine if the progression of dependency is independent of BDRS self-care scores. This would indicate that dependency and self-care capacity represent related but possibly distinct components of disability in AD.

To characterize dependence change over time, cross-tabulations were computed for dependence level and visit. This allowed us to examine the distribution of dependence level as a function of longitudinal visit. Dependence level was also examined with GEE analysis to characterize the average rate of change over time.

Finally, Cox regression analysis was used to determine endorsement of the scale items. Survival curves were generated for 3 representative scale items, corresponding to mild ("Does the patient need frequent help finding misplaced objects?"), moderate ("Does the patient need to be watched when awake?"), and severe ("Does the patient have to be fed?") levels of dependence. The 3 items were selected from 3 clearly defined subscales,⁷ representing mild, moderate, and severe dependence. Survival curves were plotted to demonstrate differential progression of each of these 3 items. Results are presented as mean \pm SD.

pendency over time. A secondary purpose was to examine the progression of patient dependence in the context of both cognitive and other functional domains.

RESULTS

At baseline, the mMMSE score was 37.72 ± 5.46 , indicating a mild-to-moderate level of cognitive impairment. Patients ranged in age from 50 to 99 years (73.0 ± 9.2 years). Patients had, on average, 13.1 ± 3.7 years of education, and 61% were female.

Examination of the baseline Dependence Scale revealed that the sum of the items was 5.31 ± 2.15 , indicat-

ing a mild level of patient dependency. Similarly, most participants were rated at dependence level 2. **Figure 1** displays the distribution of baseline dependence level ratings. All patients had at least 2 semiannual longitudinal visits, with a mean of 6.48 ± 5.13 visits.

Results of the GEE analysis revealed that the sum of the Dependence Scale changed significantly over time (estimated $\beta = 0.51 \pm 0.02$, $P < .001$), with an increase of approximately 0.5 points per 6-month interval. A similar pattern emerged when the mMMSE score at each visit was held as a covariate. Although mMMSE scores significantly changed over time (estimated $\beta = -0.13 \pm 0.01$), the change in dependency score was independent of

Table 1. The Dependence Scale*

Item	Question
A	Does the patient need reminders or advice to manage chores, do shopping, cooking, play games, or handle money?
B	Does the patient need help to remember important things such as appointments, recent events, or names of family or friends?
C	Does the patient need frequent (at least once a month) help finding misplaced objects, keeping appointments, or maintaining health or safety (locking doors, taking medication)?
D	Does the patient need household chores done for him/her?
E	Does the patient need to be watched or kept company when awake?
F	Does the patient need to be escorted when outside?
G	Does the patient need to be accompanied when bathing or eating?
H	Does the patient have to be dressed, washed, and groomed?
I	Does the patient have to be taken to the toilet regularly to avoid incontinence?
J	Does the patient have to be fed?
K	Does the patient need to be turned, moved, or transferred?
L	Does the patient wear a diaper or a catheter?
M	Does the patient need to be tube fed?

*Items A and B are coded as follows: no, 0; occasionally (ie, at least once a month), 1; frequently (ie, at least once a week), 2. The other items are coded as follows: no, 0; yes, 1.

mMMSE score (estimated $\beta=0.20\pm 0.0$). The BDRS self-care covariate factor also changed significantly with time (estimated $\beta=0.70\pm 0.02$, $P < .001$), but did not eliminate the significant change in dependency scores (estimated $\beta=0.16\pm 0.01$, $P < .001$).

Cross-classification of dependence level with visit demonstrated that rankings reflected progressively increased dependency with time. At baseline, most patients were ranked at level 2. However, by visit 3, most patients were ranked at level 3, and by visit 8, most patients were ranked at dependency level 5. **Figure 2** displays the distribution of dependence level for 6 representative longitudinal visits. When GEE analysis was used to examine dependence level, there was significant change over longitudinal visits ($P < .001$). Consistent with the cross-classification, the estimated β was 0.17 ± 0.005 , indicating that AD patients in this cohort changed dependence level approximately every 3 years.

Finally, survival analysis revealed differential endorsement of each scale item. More than 75% of the participants endorsed items A, B, and C within 1 year of baseline. Furthermore, the number of years in which most participants endorsed the other items generally increased with each consecutive scale item (**Table 2**). Survival curves for the 3 scale items representing mild, moderate, and severe dependence also demonstrated varying rates of endorsement over time (**Figure 3**). Within 1 year of the baseline visit, 50% of the participants endorsed the mild item ("Does the patient need frequent help finding misplaced objects?"). Approximately 2 years following the baseline visit, 50% of participants endorsed the moderate item ("Does the patient need to be watched when awake?"). The severe item ("Does the patient have to be fed?") was endorsed by 50% of the participants approximately 6 years following baseline.

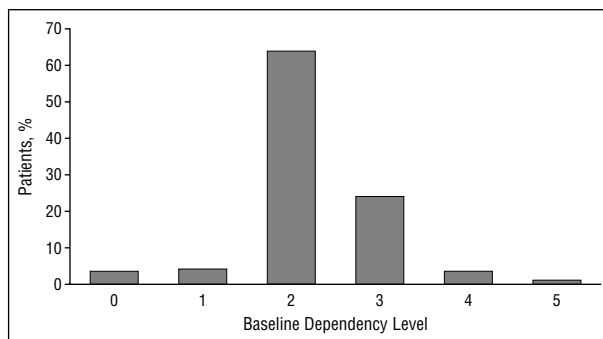


Figure 1. Baseline dependency level. Samples sizes are as follows: level 0, n=8; level 1, n=9; level 2, n=147; level 3, n=56; level 4, n=8; and level 5, n=2.

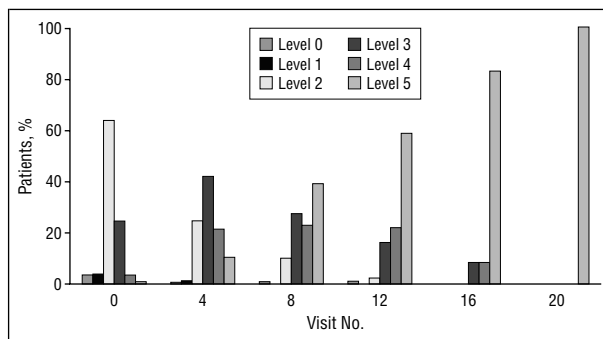


Figure 2. Percentage distribution of dependence level at each visit. Sample sizes are as follows: visit 0 (baseline), n=230; visit 4, n=155; visit 8, n=110; visit 12, n=87; and visit 20, n=1.

COMMENT

The course of patient dependency in AD was examined by analysis of the longitudinal change in Dependence Scale scores. We demonstrated that the sum of dependency items increases approximately one point per year. This increase is independent of changes in both measures of global cognition and change in BDRS scores. Similarly, we found that dependence level increases at the rate of approximately one level per 3 years.

The findings further support the validity of the Dependence Scale. Specifically, dependency scores reflected increased impairment with the progression of the disease. Furthermore, the significance of change in dependency over time was not removed when we controlled for BDRS self-care deficits. Although both scales clearly tap into areas of functional impairment, this finding indicates that they measure distinct but related components of disability in AD. Similarly, the decline in patient dependency was independent of global cognition as measured by the mMMSE. It is well established that functional and noncognitive symptoms are poorly correlated with cognitive symptoms in AD.^{29,30} Thus, it is not surprising that there is a significant decline in dependency that is not completely accounted for by a decline in global cognition. An important implication of our findings is that patient dependency is a relevant functional domain that should be considered in behavioral studies of AD and new treatment trials.

Although most studies that have used the Dependence Scale have used dependence level as a dependent

Table 2. Summary of Survival Curve Analyses of the Dependence Scale*

Dependence Scale Item	Mean (SE) No.		
	Years After Baseline at Which 25% of Subjects Endorsed Item	Years After Baseline at Which 50% of Subjects Endorsed Item	Years After Baseline at Which 75% of Subjects Endorsed Item
D	...	0.45 (0)	1.26 (0.17)
E	0.58 (0.07)	1.49 (0.09)	2.67 (0.23)
F	...	1.06 (0.16)	2.51 (0.28)
G	0.99 (0.16)	1.97 (0.20)	3.93 (0.32)
H	1.77 (0.14)	2.97 (0.20)	4.63 (0.37)
I	2.41 (0.17)	3.97 (0.34)	5.92 (0.29)
J	3.50 (0.32)	5.57 (0.27)	7.65 (0.38)
K	4.49 (0.26)	6.04 (0.32)	8.07 (0.43)
L	2.92 (0.25)	4.49 (0.50)	6.52 (0.18)
M	9.07 (0.86)	10.00 (0.34)	...

*More than 75% of the subjects endorsed items A, B, and C within the first year after baseline. Ellipses indicate data not applicable.

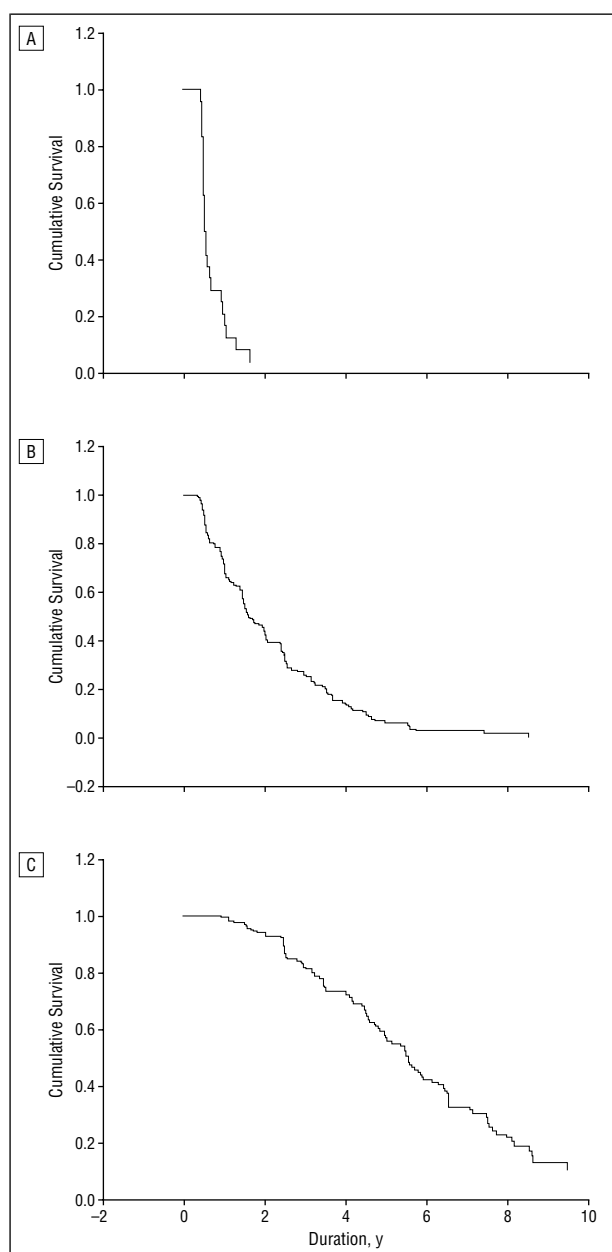


Figure 3. Survival curves for item C (“Does the patient need frequent help finding misplaced objects, keeping appointments, or maintaining health or safety?”) (A), item E (“Does the patient need to be watched or kept company when awake?”) (B), and item J (“Does the patient have to be fed?”) (C).

measure, our study suggests an alternative scoring. The sum of the items on the scale provides a measure more sensitive to change than dependence level. The sum of items score might therefore be more appropriate for short-duration clinical trials and behavioral studies. Alternatively, the *dependence level* may be an appropriate baseline covariate for similar types of research. In this vein, dependence level serves as a staging score for patient dependency, much like the Clinical Dementia Rating Scale³¹ does for overall disease severity. Also like the Clinical Dementia Rating Scale, dependence level can be useful for clinical characterization.

The survival curve analysis of 3 representative scale items mirrors the finding by Stern et al⁷ that the Dependence Scale taps into varying degrees of patient dependence. Specifically, we demonstrated that the requirement of assistance of AD patients to locate misplaced objects occurs early in the progression of the disease, whereas more time elapses before the typical patient needs to be watched and fed. Factor analysis⁷ revealed that the scale assesses 3 factors: cognitive support (items A through D); assistance, elder active (items E through I); and assistance, elder passive (items J through M). The current study suggests that each of the 3 factors occurs sequentially.

Accepted for publication January 31, 2002.

Author contributions: Study concept and design (Drs Albert and Stern); acquisition of data (Ms Riba and Drs Albert and Stern); analysis and interpretation of data (Mr Brickman, Ms Riba, and Drs Brandt and Stern); drafting of the manuscript (Mr Brickman and Dr Stern); critical revision of the manuscript for important intellectual content (Mr Brickman, Ms Riba, and Drs Marder, Albert, Brandt, and Stern); statistical expertise (Mr Brickman and Dr Stern); obtained funding (Dr Stern); administrative, technical, and material support (Mr Brickman, Ms Riba, and Drs Albert and Stern); study supervision (Dr Stern).

This study was supported by National Institutes of Health (Bethesda, Md) federal grants AG07370 and RR00645.

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