Influence of behavioral symptoms on rates of institutionalization for persons with Alzheimer's disease

D. W. GILLEY*, J. L. BIENIAS, R. S. WILSON, D. A. BENNETT, T. L. BECK
AND D. A. EVANS

Rush Institute for Healthy Aging and Rush Alzheimer's Disease Center, Chicago, IL, USA; Departments of Internal Medicine and Neurological Sciences, Rush University Medical Center, Chicago, IL, USA

ABSTRACT

Background. Recent studies indicate that behavioral symptoms may play a key role in decisions to institutionalize persons with Alzheimer's disease (AD), but the specific types of behavior that contribute to this increased risk have not been reliably identified. The relationship between behavioral symptoms and time to institutionalization was evaluated in a 4-year longitudinal study.

Method. A total of 410 persons with the clinical diagnosis of AD completed annual clinical evaluations to assess cognitive impairment, functional limitations, delusions, hallucinations, depressive symptoms and physical aggression. Participation rates among survivors exceeded 90 % for four follow-up evaluations with complete ascertainment of mortality and institutionalization. Time to institutionalization was evaluated using proportional hazards regression models in relation to time-varying clinical features.

Results. In multivariate models, adjusted for demographic and social variables, four clinical features emerged as the predominant predictors of institutionalization: cognitive impairment level, physical aggression, hallucinations and depressive symptoms. These associations were virtually unchanged in analyses controlling for mortality.

Conclusions. Specific behavioral symptoms are important independent risk factors for institutionalization in persons with AD. Because behavioral symptoms are susceptible to therapy, efforts to modify or prevent these symptoms deserve careful consideration as a means to delay institutionalization for persons with this disease.

INTRODUCTION

There is a high prevalence of Alzheimer's disease (AD) in persons over age 65 in North America and Europe. AD is a neurodegenerative condition associated with impaired cognitive function, physical disability and abnormal patterns of behavior. These debilitating effects often lead to nursing home placement (Smith *et al.* 2000), a major component of the public health costs attributable to this disease (Ernst & Hay, 1994). Thus, risk factors for institutionalization in persons with AD are important to identify in order to anticipate the demand for services and to develop interventions.

A major focus of previous AD studies has been the relationship of disease characteristics to nursing home placement. Many studies have shown that the risk of institutionalization is greater among persons with more severe cognitive impairment (Fratiglioni *et al.* 1994; Severson *et al.* 1994; Heyman *et al.* 1997). Because the level of cognitive impairment provides an index of disease severity, these findings suggest

* Address for correspondence: Dr David W. Gilley, Rush Institute for Healthy Aging, 1645 W. Jackson Blvd. – Suite 675, Chicago, IL 60612, USA.
(Email: David_Gilley@rush.edu)

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that the likelihood of nursing home placement increases systematically over the course of the disease. Recent studies also provide evidence that behavioral and affective symptoms may play a key role in decisions to institutionalize persons with AD (Smith *et al.* 2001; Yaffe *et al.* 2002). However, the types of behavioral and affective symptoms that contribute to this increased risk have not been reliably identified. Some published reports emphasize aggressive behavior (Knopman *et al.* 1988; O'Donnell *et al.* 1992; Haupt & Kurz, 1993), psychotic symptoms (Steele *et al.* 1990; Stern *et al.* 1997), or depression (Haupt & Kurz, 1993) as important predictors of institutionalization in persons with dementia. Few studies assessed more than one of these features and their findings varied substantially. Null findings are difficult to interpret because of the small samples and brief follow-up periods ($\leqslant 2$ years) used in most previous studies. Behavioral symptoms were also only measured at a single point in time, limiting inferences regarding the temporal relationship with nursing home placement.

The present study prospectively evaluated the relationship between behavioral symptoms and time to institutionalization in 410 persons with AD. A wide range of clinical features and social network characteristics were measured annually over a 4-year period and used as time-varying predictors in survival models. This approach provides a direct assessment of the temporal relationship between behavioral symptoms and institutionalization, simultaneously controlling for other potential risk factors.

METHOD

Subjects

The sample consisted of 410 persons recruited through the Rush Alzheimer's Disease Center (RADC). As a dementia specialty clinic, clinical evaluations at the RADC were conducted for initial diagnosis, confirmation of diagnosis or as a basis for clinical management recommendations. At study entry, participants met accepted diagnostic criteria for AD (McKhann *et al.* 1984) and lived in a community setting. Persons with severe cognitive impairment at baseline, based on Mini-Mental State Examination (MMSE; Folstein *et al.* 1975) scores below 10, were excluded to limit floor effects in clinical measures.

Clinical evaluation procedures for this cohort have been previously described (Wilson *et al.* 2000*a*). As a consecutive series over a 12-month period, 491 persons met eligibility requirements and 410 (83%) were recruited into the study. Study procedures, privacy protections, and informed consent were approved by the Institutional Review Board at Rush University Medical Center. Signed consent was obtained from participants and a family member.

Measures

Study data were collected during 1992–1997. Time to institutionalization is the dependent variable in these analyses, which is defined as the interval (in months) from baseline assessment to initial entry into a long-term care facility. Institutionalization was assessed by informant interview at each follow-up observation. Information on each event included the facility name and address and dates of entry and discharge. If the informant was unable to provide the exact date of entry, consent was obtained to contact the long-term care facility for this information. Nursing home placement was also assessed if the participant had died since the last observation. This method provides a cumulative record of nursing home placement from baseline to the final follow-up observation. Informants provided complete ascertainment of institutionalization and mortality during the study; missing observations were limited to clinical evaluation variables.

Clinical features were assessed at baseline and up to four follow-up evaluations (participation rates ranged from 90·9% to 95·1%, see Wilson *et al.* 2000*a*). Follow-up evaluations were identical to baseline procedures except that follow-up examinations were conducted in the participant's home. Examiners were blind to all previously collected data. Structured interviews with an informant were used to collect all study data except for cognitive performance tests. For each observation, the person with the most frequent contact with the participant was selected as informant.

Behavioral symptoms

Four behavioral symptoms, each associated with institutionalization in some prior studies, were assessed: depressive symptoms, hallucinations, delusions and physical aggression. Depressive

symptoms were assessed using the 17-item Hamilton Rating Scale (HRS: Hamilton, 1960), with scores ranging from 0 to 56. Specific implementation of the HRS was based on the structured interview format (Gilley *et al*. 1995). The presence of delusions as false, fixed beliefs was assessed using seven questions (Wilson *et al*. 2000*b*), covering the subtypes of persecutory, grandiose, somatic and jealous delusions. The presence of hallucinations was assessed using four questions (Wilson *et al*. 2000*b*), covering visual and auditory indications of events not perceived by others present. Misinterpretations of environmental stimuli were not included as hallucinations. Physically aggressive behavior was limited to interpersonal violence and did not include threats to harm, gestures and actions confined to objects. The presence of physical aggression (Ryden, 1988) was based on endorsement of any of four categories of interpersonal violence: strike with hand or foot; strike with an object or weapon; push, shove or knock down; and take hold by squeezing, pinching or biting.

Demographic information and other clinical characteristics

Demographic information collected at the baseline evaluation included age, gender, race, marital status and education. Social network variables, collected at each observation, included household composition; relationship between participant and the identified primary caregiver (spouse, child, other relative, other); and number of children, other relatives and friends living within 30 min travel time, each coded on a four-point scale (0, 1–2, 3–4, >4).

The MMSE was selected as the primary index of cognitive impairment because of its widespread use in scaling dementia severity. Scores range from 0 to 30 based on the number of correct responses; thus, lower scores indicate greater severity of cognitive impairment. As a secondary measure of cognitive function, a composite score from 17 neuropsychological tests (Wilson *et al*. 2000*a*) was created. Raw scores were converted to *z* scores using baseline means and standard deviations, and then averaged to form a single composite.

Physical function was assessed using three standard self-report scales (Cornoni-Huntley *et al*. 1986), modified slightly for use as informant ratings in the present study. The 6-item Katz Activities Scale was used to measure the ability to independently perform basic self-care activities (bathing, dressing, walking across a small room, transferring from bed to a chair, using the toilet and eating); scores range from 0 to 6 based on the number of activities performed independently. The 3-item Rosow–Breslau Scale was used to measure mobility (walking a half-mile, walking up a flight of stairs and strenuous work around the house); scores range from 0 to 3 based on the number of activities performed without assistance. Five questions (Cornoni-Huntley *et al*. 1986) were use to record volume lost and frequency of urinary incontinence. Following the recommendations of Thom (1997), clinically significant urinary incontinence was defined as sufficient volume to wet the outer clothing (and readily visible to others) and occurring nearly every day.

Analytic methods

The primary objective of this study was to evaluate relations between behavioral symptoms of AD and time to institutionalization. Predictors of time to institutionalization were evaluated using proportional hazards regression models (Cox, 1972). An initial model was fit consisting of demographic and social network variables. All subsequent analyses were adjusted for age, gender, race, education, living situation and children living in the area. Each clinical variable was then evaluated individually to characterize the univariate association with time to institutionalization. Next, the full model containing all clinical variables was estimated and served as the primary basis for hypothesis testing. Finally, the most parsimonious set of clinical predictors was identified using both forward selection ($p < 0.1$ to enter) and backward elimination ($p > 0.1$ to remove) procedures. Of note, social network characteristics and clinical features were included as time-varying predictors in all analyses. Goodness of fit was checked with deviance residuals and deviations from proportionality of the hazard function for each variable over time were examined using residual plots (Collett, 1994).

RESULTS

At baseline, all participants resided in the community. The sample was predominantly female

Table 1. *Summary of clinical characteristics at baseline evaluation and at last available evaluation*

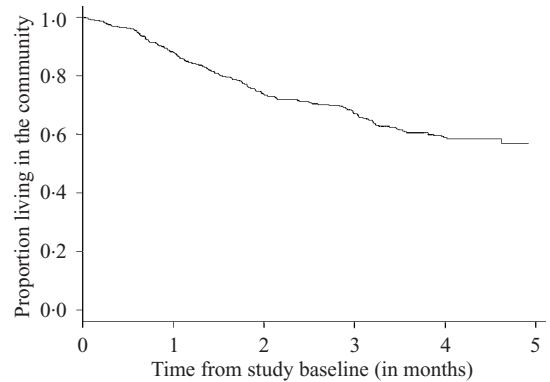| Clinical characteristic	Baseline evaluation	Last available evaluation
MMSE score (mean, S.D.)	18·7 (7·1)	11·8 (7·4)
Katz ADL (mean, S.D.)	4·8 (1·2)	3·4 (2·1)
Rosow–Breslau (mean, S.D.)	2·6 (0·7)	1·6 (1·8)
HRS Depression score (mean, S.D.)	10·1 (6·8)	9·5 (6·4)
Urinary incontinence, n (%)	29 (7·1)	101 (27·1)
Hallucinations, n (%)	184 (45)	179 (47·9)
Delusions, n (%)	168 (55·2)	208 (55·7)
Physical aggression, n (%)	21 (5·1)	45 (12·1)

FIG. 1. Kaplan–Meier curve showing the proportion of the sample living in a community setting over the study period, adjusted for censoring due to mortality.

(59·1%), white (84·9%), and well educated (65% completed 12 or more years of formal education). Age ranged from 45 to 95, with mean of 75·5 (S.D. = 7·3) years. Most participants resided with a spouse (48·3%) or child (29·8%) during the study period; 21·9% lived alone at the time of the baseline evaluation and only 4% lived alone at the final observation. Table 1 summarizes clinical characteristics at baseline and at the last clinical evaluation prior to entry into a nursing home or death. A total of 155 participants entered a nursing home during the observation period, an overall rate of 0·12 per person-year of observation and a median time to institutionalization of 3·3 years. Fig. 1 describes the temporal pattern of institutionalization with a Kaplan–Meier survival curve, which reflects the proportion of patients living in the community over the study period.

The first step in the analysis was to evaluate demographic and social network characteristics as predictors of time to institutionalization. Marital status and living situation were combined into three categories, with living with a spouse used as reference condition and separate contrasts for living alone and living with a child. Among demographic variables, male gender [Relative Risk (RR) 1·64; 95% confidence interval (CI), 1·12–2·41] and higher educational attainment (per year increase, RR 0·92; 95% CI 0·89–0·99) were the only variables associated with increased risk of institutionalization. Substantial effects were also observed for two variables related to the availability of informal caregivers, living alone (RR 1·92; 95% CI 1·25–2·96) and number of children living in the area (within 30 min travel time) (per category,

RR 0·61; 95% CI 0·47–0·79). Time to institutionalization was comparable for participants living with a spouse and those living with a child. Likewise, institutionalization was not associated with the presence of relatives other than children or of close friends in the area.

Table 2 presents the results of proportional hazards regression models testing each clinical feature individually as a predictor of time to institutionalization, after adjustment for demographic and social network variables. All clinical features were significantly associated with increased risk of institutionalization. However, in the full model testing all clinical features simultaneously, the magnitude of association with institutionalization was substantially attenuated for the disability measures, urinary incontinence and delusions. Only the level of cognitive impairment on the MMSE, the presence of physical aggression, the presence of hallucinations and the level of depressive symptomatology on the HRS remained significant. To evaluate the stability of this predictor set, stepwise procedures (forward selection and backward elimination) were used. These sequential selection procedures produced identical results, identifying cognitive impairment level, physical aggression, hallucinations and depressive symptoms as the most parsimonious set of predictors of time to institutionalization. Finally, the results of these analyses were unchanged when a composite measure of cognitive function, based on an average z score for 17 neuropsychological tests, was substituted for the MMSE (data not shown).

Table 2. *Proportional hazards models of time to institutionalization using clinical features as predictors. Variables were evaluated as single predictors in univariate models, together in a full model, and together in trimmed best predictive model. Effects are summarized as relative risks (RR) with 95% confidence intervals (95% CI)*

Predictor	Univariate model*		Full model*		Trimmed model*	
	RR	95% CI	RR	95% CI	RR	95% CI
MMSE	0·93	0·91–0·96	0·95	0·93–0·98	0·95	0·92–0·97
Katz ADL	0·79	0·73–0·86	0·94	0·82–1·07	—	
Rosow–Breslau	0·82	0·70–0·95	1·02	0·85–1·23	—	
Urinary incontinence	1·93	1·28–2·91	1·17	0·72–1·90	—	
Physical aggression	4·17	2·67–6·50	2·30	1·41–3·76	2·30	
Hallucinations	2·54	1·82–3·54	1·83	1·27–2·63	1·85	1·41–3·72
Delusions	1·40	1·12–1·87	0·81	0·56–1·18	—	1·30–2·64
HRS Depression	1·07	1·05–1·10	1·04	1·01–1·08	1·04	

* All models adjusted for age, gender, race, education, living situation and number of children living within 30 min travel time.

A total of 149 persons died during the follow-up period, including 84 prior to institutionalization, raising the possibility that death may have been an important competing endpoint. To evaluate this possibility, the full model (Table 2) was computed excluding these 84 participants. Coefficients for gender, living arrangements, education, MMSE, hallucinations, physical aggression and depression remained significant and relatively unchanged in magnitude. Coefficients for age, activities of daily living on the Katz scale, and urinary incontinence approached significance ($p = 0.150$–0.185), indicating that mortality slightly attenuated the effects of these variables. To further explore the effect of mortality, a series of sensitivity analyses (Allison, 1985) were performed using the full model (Table 2) for comparison. In one series, time to the first event (death or institutionalization) was modeled. In another series, the 84 persons who died prior to entering an institution were censored at the study endpoint, which treats death as a protective factor. The overall pattern of significant effects in each of these analyses remained unchanged from the original model.

DISCUSSION

Avoidance of premature entry into nursing homes for persons with AD is recognized as a central goal by families of affected persons and by health-care policy makers. The results of this longitudinal study suggest that three specific behavioral symptoms are strongly associated with increased risk of institutionalization in persons with AD: physical aggression, hallucinations and depressive symptoms. These behavioral symptoms independently reduce survival time in the community, even controlling for other personal and disease characteristics. Both physical aggression and hallucinations were associated with an approximately two-fold increase in the risk of institutionalization. Likewise, a 10-point increase in depressive symptoms on the HRS was associated with a 40% increase in the risk of institutionalization. These findings extend current knowledge by highlighting differences in the risk of institutionalization attributable to specific patterns of behavior. Because these behavior patterns are potentially susceptible to therapy (Allen & Burns, 1995), efforts to modify or prevent them deserve careful consideration as a possible means to delay institutionalization for persons with AD, along with interventions aimed at providing information and support to family caregivers (Brodaty *et al.* 1993; Mittelman *et al.* 1996).

The present study has several strengths. First, statistical power was enhanced by the inclusion of over 400 persons with the clinical diagnosis of AD and a 4-year follow-up period. Second, the high rate of follow-up participation reduces the risk of bias due to selective attrition. Third, clinical variables were assessed annually and included as time-varying predictors, which provides a more direct evaluation between current status and entry into an institution.

There are, however, several important limitations that need to be considered in interpreting the results of this study. First, the sample was derived from an AD specialty clinic. Only a small percentage of persons with AD come to medical attention (Ross *et al.* 1997), typically cases with more severe disease manifestations. Additional selection factors may influence the decision to seek evaluation at a specialty clinic. Thus, population-based studies are needed to establish the generality of these findings. The use of an incident disease cohort would also permit characterization of institutionalization rates across the entire disease course from the initial onset of symptoms.

Second, clinical evaluations in the study were conducted at one-year intervals. Although this procedure is adequate to characterize changes in cognitive and physical function, it may be less efficient in capturing variables with sporadic patterns of expression, most notably the behavioral symptoms. For example, episodes of physical aggression are infrequent, on average occurring at a rate of only 0·1 episodes per month (Gilley *et al.* 1997). Thus, the effects of behavioral symptoms are likely to be underestimated in the present study.

Finally, measures of several potentially important factors were not included in the present study. Without a measure of instrumental activities of daily living (e.g. telephone use, management of finances), variance attributable to functional status may not have been captured fully in the study. The focus of this study was exclusively on measures of disease symptoms. However, family caregivers are often the final common pathway in decisions to enter an institution with the impact of clinical symptoms on caregivers as an important mediator variable in this process (Yaffe *et al.* 2002). Physical aggression has been associated with increased caregiver depression (Nagaratnam *et al.* 1998), but the unique contribution of other behavioral symptoms to caregiver distress remains uncertain. Because caregiver depression was not assessed, we cannot examine caregiver distress as an explanatory mechanism for our findings. It is also possible that caregiver distress may bias ratings of behavioral symptoms. Thus, the role of caregiver adjustment is an important area for future study in understanding why specific behavioral symptoms uniquely contribute to long-term care utilization in persons with dementia.

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