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Prevalence and Impact of Medical Comorbidity in Alzheimer's Disease

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Background. We examined the prevalence of comorbid medical illnesses in Alzheimer's disease (AD) patients at different severity levels. We also examined the effect of cumulative medical comorbidity on cognition and function.

Methods. Analyses of data from 679 AD patients (Mini-Mental State Exam score range 0–30, mean ± *SD* = 11.8 ± 8) from 13 sites (four dementia centers assessing outpatients, four managed care organizations, two assisted living facilities, and three nursing homes) prospectively recruited using a stratification approach including dementia severity and care setting. Medical comorbidity was quantified using the Cumulative Illness Rating Scale-Geriatric.

Results. Across patients, 61% had three or more comorbid medical illnesses. Adjusting for age, gender, race, and care setting, medical comorbidity increased with dementia severity (mild to moderate, $p < .01$; moderate to severe, $p < .001$). Adjusting for age, educational level, gender, race, and care setting, higher medical comorbidity was associated with greater impairment in cognition ($p < .001$) and in self-care ($p < .001$).

Conclusions. Despite the limitation of a cross-sectional design, our initial findings suggest that there is a strong association between medical comorbidity and cognitive status in AD. Optimal management of medical illnesses may offer potential to improve cognition in AD.

RELATIVELY few studies have examined the prevalence of comorbid medical conditions in Alzheimer's disease or the interactions between cognition and physical illness (e.g., 1–2). Cognitive impairment in Alzheimer's disease may potentially lead to inaccurate symptom reporting, noncompliance, and delayed or inadequate treatment. Conversely, physical illnesses and medications may potentially impact cognition or neurodegeneration. In this report, we use data from a multisetting survey of Alzheimer's disease patients to examine the prevalence of medical comorbidity and its effects on cognition and function.

Methods

Subjects and Assessments

This cross-sectional survey recruited 679 Alzheimer's disease patients and caregivers from 13 sites [four managed care organizations, four medical centers, three nursing homes (NHs), and two assisted living facilities (ALFs)] in nine states. Patients were stratified by care setting and dementia severity. The study was approved by the Institutional Review Boards at each institution, and written informed consent was obtained from family caregivers and, where possible, the patient. Key inclusion criteria were National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable Alzheimer's disease; at least 50 years of age; receiving care from one of the four settings; and family caregiver willing to participate in the study. The community sample reflected consecutively enrolled patients who met study criteria. The NH and ALF samples consisted of all current residents who met criteria. Other details of this sample have been published (3).

After investigator training, demographic, clinical, and cognitive data were collected using interviews with both patients and the primary family or institutional caregiver. The Clinical Dementia Rating Scale (CDR) (4) was used to stage the severity of the dementia using interviews with the patient and caregiver. For some analyses, the six categories of the overall CDR score were collapsed into mild (questionable and mild), moderate, and severe (severe, profound, and terminal). The Cumulative Illness Rating Scale–Geriatric (CIRS-G) rates 14 organ systems on a 5-point scale where 0 indicates no problem and 4 indicates severe problems. We used the three summary measures (total number of endorsed categories, sum of scores across the endorsed categories, and the severity index [the total score divided by number of categories]) that have been previously validated (5,6). At sites, the CIRS-G was completed by reviewing patient medical histories, past records, and physical examinations. Physical examinations were also conducted for those subjects who had not had one recently. In calculating the CIRS-G summary measures, the psychiatric illness category is excluded because in the CIRS-G, Alzheimer's disease is classified as a psychiatric illness. The Mini-Mental State Examination (MMSE) was performed within two weeks of the disease

staging with the CDR. Mobility and self-care were measured using subscales of the Health Utilities Index (7).

Statistical Analyses

The present analyses used *t* tests, chi-square analysis, and the general linear model (GLM) procedure in SAS. Results from the least square means from the GLM program were tested for differences across the comorbidity measures and for differences in the distribution of specific illness categories between severity levels. To examine the effect of comorbidity on cognition, we ran three GLM models. The first tested the effect of age, education, and care setting. The second model introduced the CIRS-G Severity Index; the third introduced the interaction between the CIRS-G Severity Index and age. These same models were also run for incontinence, mobility, and self-care, with the addition of cognition (MMSE) as another independent variable.

Results

Table 1 summarizes the characteristics of the sample. Of the 679 patients, 354 were in the community (mean age 87 ± 7 years, mean MMSE 16 ± 8), 161 were in ALFs (83 ± 7 years, 9 ± 8), and 164 resided in NHs (77 ± 8 years, 6 ± 7). Fifty-four percent of community patients had mild dementia, whereas 53% of NH patients had severe dementia. Compared to NH and ALF residents, community patients were younger ($p < .001$), more likely to be male ($p < .001$), to be married (69% vs 26% vs 15%, $p < .001$), to have spouse caregivers (63% vs 20% vs 7%, $p < .001$), to have lower Alzheimer's disease severity levels ($p < .001$), and to have higher MMSE scores ($p < .001$). Compared to NH residents, residents in ALFs were younger ($p < .001$), had higher educational levels ($p < .001$), were more likely to be married ($p < .001$), to have spouse caregivers ($p < .001$), and present lower Alzheimer's disease severity levels ($p < .001$) and higher MMSE scores ($p < .001$).

Unadjusted, on average, Alzheimer's disease subjects had more than three conditions (3.3 endorsed categories), a CIRS-G Severity Index of 1.9, and a CIRS-G Total Score of 5.5. After adjustment for care setting, dementia severity, age, gender, educational level, and race, all three summary CIRS-G measures were higher for residents in NHs or ALFs compared to patients in the community ($p < .001$). Adjusting for age, gender, race, and care setting, medical comorbidity increased with dementia severity (mild to moderate, $p < .01$; moderate to severe, $p < .001$). Adjusted CIRS-G Index and Total Scores were higher in the severe stage compared to the moderate and mild stages ($p < .001$). The number of Endorsed Categories and adjusted total CIRS scores also increased with age ($p < .001$). CIRS-G scores did not significantly differ between men and women or between whites and nonwhites.

Table 1. Alzheimer's Disease Sample Characteristics by Service Setting ($N = 679$)

Characteristic	Community Patients ($n = 354$)	Assisted Living Residents ($n = 161$)	Nursing Home Residents ($n = 164$)
Mean Age	77.1 [8.18]	82.6 [7.03]	86.6 [7.20]
Gender: Female, %	55.6	75.8	83.5
Race: White, %	85.9	96.3	89.6
Years of Schooling, *M* [*SD*]	12.3 [4.09]	12.1 [3.82]	10.5 [4.48]
Married, %	69.2	25.5	14.6
Spouse Caregiver, %	63.3	19.3	6.7
MMSE Score, *M* [*SD*]	15.7 [7.93]	9.1 [7.64]	5.9 [6.83]
Dementia Severity, %			
Mild	54.0	27.9	6.1
Moderate	30.5	34.2	40.9
Severe	15.5	37.9	53.0

Notes: See text for details of statistical differences between groups. Severity was determined using the Clinical Dementia Rating Scale. MMSE = Mini-Mental State Exam.

At least 45% of all patients had musculoskeletal, genitourinary, and/or ear, nose, and throat (ENT) disorders; at least 30% had vascular/heart diseases; and at least 25% had lower gastrointestinal tract and/or endocrine/metabolic disorders (Figure 1). When patients were grouped by dementia severity level, genitourinary disorders were substantially greater among patients in the severe stage (69%) compared to those in the mild (48%; $p < .001$) and the moderate stages (48%; $p < .001$). ENT disorders were more prevalent in moderate than in severe stages ($p < .001$).

After adjusting for age, gender, education, and care setting, higher medical comorbidity was associated with lower MMSE scores ($p < .0001$). The total explained variance of the complete model (R^2) was 0.34. Although the influence of medical comorbidity on reducing cognition was partially mediated through its association with age, education, gender, and care setting (Figure 2), increased medical comorbidity showed an independent effect on cognition. After controlling for age, gender, education, care setting, and cognition, higher medical comorbidity was also associated with poor self-care ($R^2 = .47$, $p < .0001$), decreased mobility ($R^2 = .25$, $p < .0001$), and greater incontinence ($R^2 = .48$, $p < .0002$). The effect of the interaction between CIRS-G severity index and age on these measures was significant only for incontinence ($p < .0001$).

Discussion

To our knowledge, this is the first published study to report the stage-specific prevalence of medical conditions in mild, moderate, and severe stages of Alzheimer's disease as well as in patients at different care settings. Several findings emerged from this study that complement and extend the prior literature in this area. For example, McCormick and colleagues (1) used a population-based dementia registry to compare comorbidity and symptoms reported by 154 clinically diagnosed, probable Alzheimer's disease cases with two control groups (92 nondemented subjects with mild cognitive impairments and 129 cognitively intact controls) frequency-matched for age and gender. They reported that symptoms of cognitive impairment were more frequent in Alzheimer's cases. However, complaints related to other body systems (e.g., gastrointestinal symptoms, joint pain, vision problems) were less common in Alzheimer's cases than in controls even though comorbidity was similar among all three groups. They concluded that people with Alzheimer's disease may underreport common symptoms not related to cognitive impairment. Our study found that medical comorbidity was greatest in older subjects (as expected) and in se-

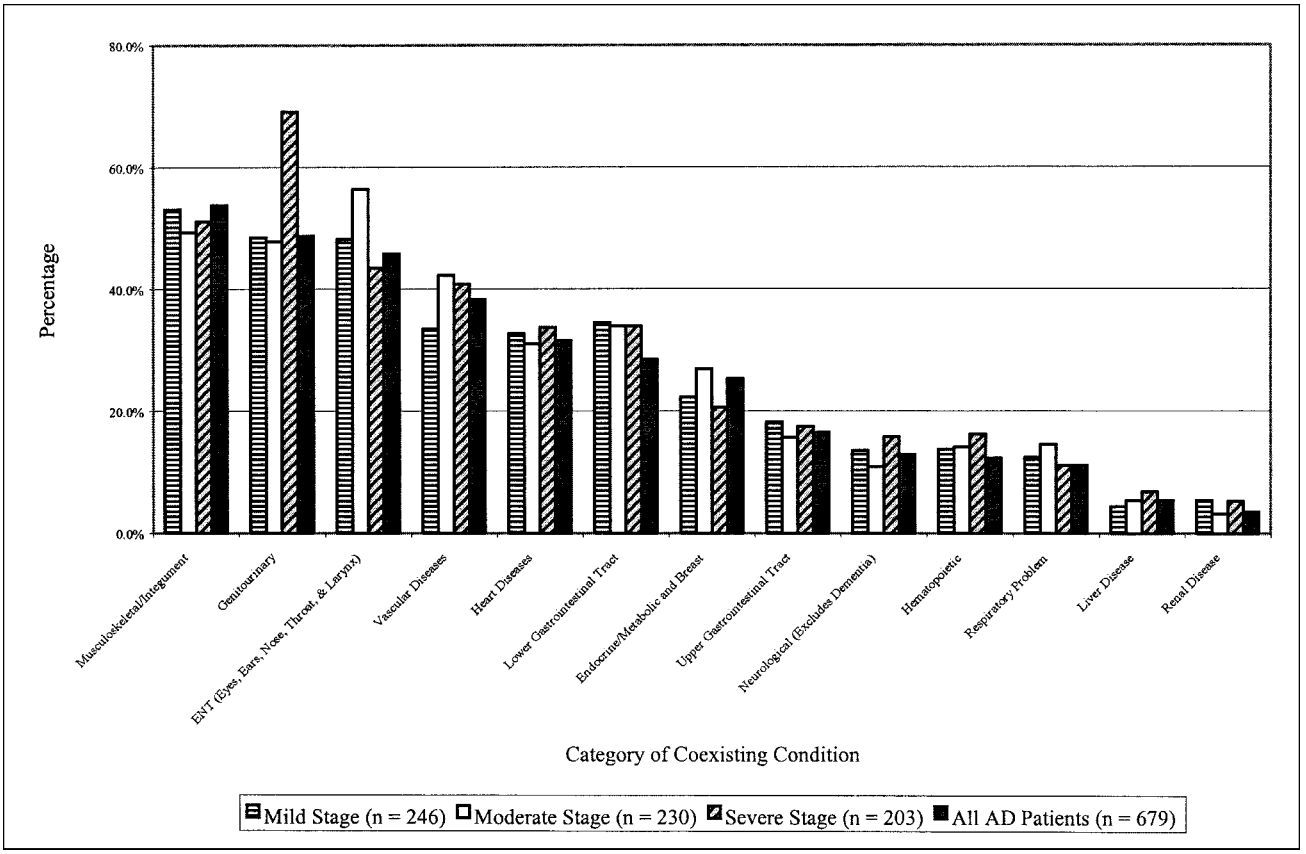

Figure 1. Percentage of all Alzheimer's disease (AD) patients with specific comorbid disease categories and by AD severity groups adjusted for care setting, age, and gender.

vere Alzheimer's disease subjects in NHs. We did not find any differences by race, gender, or education. In addition, our study found that ENT, vascular, musculoskeletal, and genitourinary disorders were the most prevalent disorders. ENT and genitourinary disorders increased with dementia severity independent of age. The findings from our study as well as those of McCormick and colleagues together suggest that clinicians should have a heightened awareness of noncognitive disorders whose symptoms may be underreported during health maintenance visits of Alzheimer's disease patients.

We also found that medical comorbidity was associated with impaired mobility and incontinence, most likely due to the high prevalence of musculoskeletal and urinary disor-

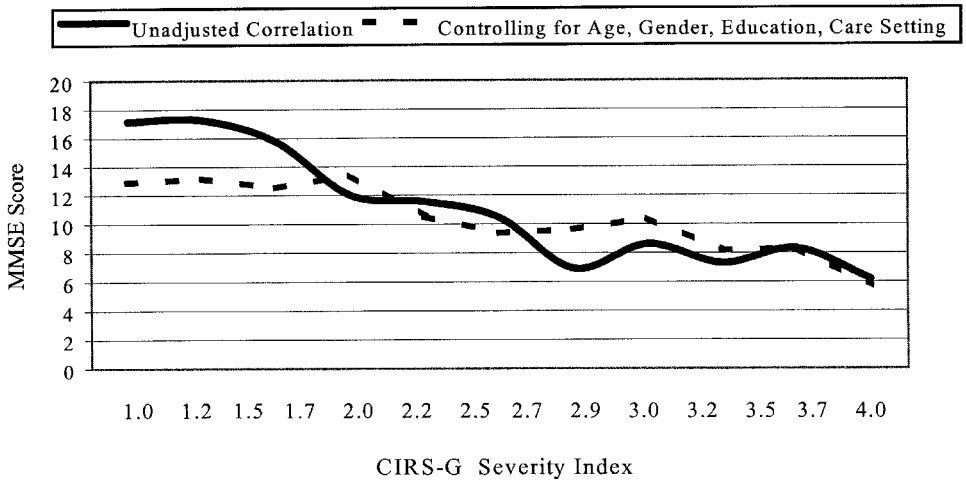

Figure 2. Mean Mini-Mental State Exam (MMSE) scores across CIRS-G Severity Index. The figure is derived using the LSMEANS procedure in the SAS general linear model program. CIRS-G = Cumulative Illness Rating Scale–Geriatric.

ders. Medical comorbidity was also independently associated with lower cognition and self-care levels. These findings add to prior studies that have evaluated the impact of comorbidities on health care utilization and mortality in Alzheimer's disease patients. Van Dijk and colleagues (2) investigated the relationship between comorbidity and survival in an 8-year follow-up study of 606 nursing home dementia patients. In this study, Parkinsonism, atrial fibrillation, pulmonary infection, and malignancies were powerful predictors of mortality and doubled the mortality chances. They also found that more severely demented patients had greater comorbidity and that comorbidity and dementia severity independently influenced mortality. In another study of community-dwelling elderly patients (not selected on the basis of presence of dementia), Shelton and coworkers (8) found that the presence of two or more comorbidities was a significant predictor of future hospitalization or emergency department visit. In addition, several studies have documented that the total cost of managing patients with Alzheimer's disease increased significantly over age- and comorbidity-matched controls without Alzheimer's disease (reviewed in 9). These extra costs have included not only nursing care, but also medical claims for outpatient care, emergency department visits, and hospitalization. Despite such evidence, underdiagnosis, coding, and reimbursement barriers often result in subjects with Alzheimer's disease receiving inadequate care (9).

The present study design cannot unravel the potential reasons for such associations between higher cumulative comorbidity and lower cognition. Speculatively, the effect of medical comorbidity on cognition in Alzheimer's disease may be due to direct effect on the brain, adverse effect of concomitant medications, and/or impaired test-taking ability. It is also possible that the relatively high prevalence of vascular disorders, such as hypertension and coronary artery disease, may have contributed to the cognitive impairments in this sample. Accumulating epidemiological and neuropathological evidence supports an association between Alzheimer's disease and several vascular risk factors, such as hypertension, coronary artery disease, diabetes mellitus, ischemic white matter lesions, and generalized atherosclerosis (10). It is speculated that vascular disease may stimulate the dementia process or affect its clinical expression. It is also of interest that one randomized controlled trial has shown that treatment of systolic hypertension can reduce the incidence of dementia (11). A nested case-control study of the United Kingdom General Practice Research Database (comprising 368 practices) found that individuals 50 years or older who were prescribed a lipid-lowering statin drug had a substantially lower risk of developing dementia (12). In addition, the apolipoprotein E4 allele, a risk factor for Alzheimer's disease, is also a vascular risk factor and has recently been associated with left ventricular dysfunction in Alzheimer's disease subjects (13). Taken together, these data argue for a heightened awareness of vascular risk factors in subjects at risk for dementia as well as in those already diagnosed with Alzheimer's disease. Prospective controlled trials are needed to determine if better identification and treatment of such risk factors may alter the onset or progression of Alzheimer's disease.

Limitations of the current data include the cross-sectional approach, which cannot confirm causality, and the observation that this sample may not necessarily be representative of all Alzheimer's disease patients. Although physical examination data were available for all subjects, such exams were not performed for all patients specifically for this study. Hence, it is possible that incomplete charting may have led to some inaccuracies in quantifying comorbidity. In addition, we did not control for the adequacy of treatment, and it is also possible that medications used to treat the comorbidities may have affected cognition, rather than the illness per se. It is well known that demented patients are sensitive to the anticholinergic side effects of a variety of medications, including some prescribed for cardiovascular, respiratory, or genitourinary conditions. The strengths of this study are the inclusion of subjects across severity levels/care settings, standardized collection of cognitive, functional, and medical measures, and the relatively large sample size.

In summary, our preliminary findings suggest that there is a strong association between medical comorbidity and cognition in Alzheimer's disease. Medical comorbidities must be given consideration in the design and interpretation of cognitive and functional studies in dementia. The inclusion of patients with representative medical comorbidity in clinical trials would allow for greater generalizability of efficacy, safety, and drug interaction profiles of the drugs being tested. At present, cholinesterase inhibitors are the only approved treatment to enhance cognition and global function in Alzheimer's disease (14). Further studies are warranted to determine whether early recognition and management of comorbid conditions, such as hypertension and coronary disease, may offer potential to further optimize cognitive and functional abilities in Alzheimer's disease. While these physical health problems are not unique to Alzheimer's disease, they may have more functional impact in adults with Alzheimer's disease (15). In addition to incorporating comorbidity as part of dementia cognitive research studies, the reduction of comorbid physical illness may also be a legitimate, independent outcome measure to target in the effectiveness of the care provided to such subjects (15). The Cumulative Illness Rating Scale–Geriatric, Charlson Index, and Greenfield Index of Coexistent Disease are some of the scales available to quantify comorbidity for such purposes (6,7,15). Given that the vast majority of managed care organizations still lack formal disease management programs for Alzheimer's disease, our findings along with those in the literature suggest a need for directed efforts to improve medical management for member subjects with Alzheimer's disease.

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