

Predictors of Subjective Memory Complaint in Cognitively Normal Relatives of Patients with Alzheimer's Disease

David H. Tsai, M.D.
Robert C. Green, M.D., M.P.H.
Kelly S. Benke, B.A.
Rebecca A. Silliman, M.D., Ph.D.
Lindsay A. Farrer, Ph.D.

The authors utilized a family-based, case-control study to identify factors predicting subjective memory complaint in relatives of Alzheimer's disease patients. The authors ascertained 1,499 cognitively healthy relatives of Alzheimer's disease patients at 15 centers, who contributed demographic and medical information, including self-assessment of memory. First-degree relatives of Alzheimer's disease patients reported subjective memory complaint more than spouses of Alzheimer's disease patients. Relatives with past depression symptoms endorsed subjective memory complaint more than those without such history. Clinicians counseling family members of Alzheimer's disease patients who express subjective memory complaint should first evaluate cognition. If cognition is intact, depression should be considered.

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A number of reports suggest that among healthy elderly persons, nearly one-third complain of memory problems.^{1–6} Clinicians often are faced with the choice of ignoring a subjective memory complaint and reassuring patients (which might lead to missing cases of early dementia) or taking such a complaint seriously (which could trigger unnecessary dementia evaluations). This dilemma may be particularly problematic with family members of patients with Alzheimer's disease. Many biological relatives of Alzheimer's disease patients recognize that they are at higher risk for Alzheimer's disease,^{7,8} and even spouses of Alzheimer's disease patients can become sensitized to the symptoms of memory impairments. Any information that helps clinicians better evaluate the likely etiology of such a complaint would be welcome.

Previous literature on subjective memory complaint has focused upon either healthy volunteers or population-based cohorts. To our knowledge, subjective memory complaint in the relatives of patients with Alzheimer's disease has not been previously examined. Because cognitively healthy relatives of patients with Alzheimer's disease are at higher risk for developing

Received February 18, 2005; accepted July 18, 2005. Drs. Tsai, Green, Silliman, and Farrer are affiliated with the Boston University School of Medicine and the Boston University School of Public Health, Boston, Massachusetts. Dr. Benke is affiliated with the Boston University School of Medicine, Boston, Massachusetts. Address correspondence to Dr. Green, Boston University School of Medicine, 715 Albany St., L-320, Boston, MA 02118; rcgreen@bu.edu (E-mail).

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Alzheimer's disease compared with non-relatives,⁷ they provide a unique opportunity to further understand this phenomenon. The goal of this study was to identify the factors associated with subjective memory complaint among cognitively healthy first-degree relatives of Alzheimer's disease patients.

METHOD

Setting and Subjects

Data for this study were collected as part of the MIRAGE study (Multi-Institutional Research in Alzheimer Genetic Epidemiology), a family-based study of genetic and environmental risk factors for Alzheimer's disease. The starting point for recruitment of MIRAGE families is the proband: a living individual with probable or definite Alzheimer's disease as defined by the National Institute of Neurological and Communication Disorders and Stroke (NINCDS)/Alzheimer's Disease and Related Disorders Association (ADRD) research criteria.⁹ Data were collected between May 1996 and March 2002 at 15 medical centers in the United States, Germany, and Canada, and this analysis utilizes 1,203 first-degree relatives and 296 spouses of Alzheimer's disease patients who were 50 years of age or older and had no history of cognitive impairment. In order to validate the reports of healthy cognitive status, the modified Telephone Instrument for Cognitive Status (mTICS)^{10,11} was administered to 1,223 of these participants. Using a cutoff score of ≥ 27 to define those with healthy cognition, only three individuals (0.2%) were questionable and thus were excluded from the analysis. Multiple informants (medical records including autopsy reports, death certificates, and nursing home records) were used where available to supplement information on both probands and first-degree relatives. The details of the MIRAGE study design, data collection procedures, and protocols for obtaining family histories have been reported elsewhere.^{7,12-15}

Data Collection

A structured questionnaire administered by trained staff was used to collect information about demographics, family, medical and social history, including one question to elicit subjective memory complaint. The subjective memory complaint question was, "Do you have trouble remembering things from one second to the

next?" Data on other potential predictors also were collected. These included history of depression symptoms and history of diabetes or heart disease. History of depression symptoms was defined as an affirmative response to the question, "Aside from normal reaction to bereavement (death in family) or the impact of a physical/medical condition, has there been a period of weeks to several months (or longer) when you were unable to perform social and occupational functions normally because of depression?"¹⁵ Age was treated as a continuous variable. Ethnicity was categorized as African-American, defined by self-report, or not categorized at all. The relationship of the participant to the Alzheimer's disease patient was characterized as first-degree kinship (e.g., parent, sibling, or child) or spouse.

Data Analysis

Multivariate models for assessing predictors of subjective memory complaint were evaluated using generalized estimating equations (GEE) with a logit link to account for the family correlation structure of the data set.¹⁶ In the multivariate model, the dependent variable was subjective memory complaint and the independent variables were relationship to the proband, history of depression symptoms, and history of diabetes or heart disease. The element of confounding was evaluated by assessing models with different combinations of covariates and examining the change in association with subjective memory complaint. Odds ratios with 95% confidence intervals (CI) were derived. All analyses were performed using SAS system, v8.2 (SAS Institute, Cary, NC), with PROC GENMOD for GEE modeling.

RESULTS

Table 1 shows the characteristics of the 1,499 participants according to response to the subjective memory complaint question. One hundred thirty-four (8.9%) cognitively healthy relatives (this figure includes both first-degree relatives and spouses) answered "yes" to the subjective memory complaint question. Participants who endorsed subjective memory complaint were similar in mean age and sex distribution to those who did not.

Multivariate analysis (Table 2) revealed that first-degree relatives were significantly more likely to report subjective memory complaint than spouses (odds ratio = 1.9, 95% CI 1.3, 3.0). Relatives with a history of de-

pression symptoms were more likely to report subjective memory complaint than those without such history (odds ratio = 3.5, 95% CI 2.1, 5.7). A history of either diabetes or heart disease was not significantly associated with subjective memory complaint.

DISCUSSION

Both first-degree biological kinship and depression symptoms were predictors of subjective memory complaint in cognitively healthy family members of patients with Alzheimer's disease. First-degree relatives were nearly twice as likely to report subjective memory complaint, and relatives reporting a history of depression symptoms were more than three times as likely to report subjective memory complaint. Subjective memory complaint has been associated with increased risk of subsequent dementia in some, but not all studies. In a large

sample of healthy elderly Dutch, subjective memory complaint was significantly associated with the development of dementia within 3 years.¹⁷ This association was stronger in those subjects who had both memory complaints and poor memory performance. In an Australian community sample, subjective memory complaint did not appear to predict cognitive change or the development of dementia over nearly 4 years of follow-up, once anxiety and depression symptoms were taken into account.¹⁸ However, we found the opposite results when we reanalyzed their data with more sophisticated modeling techniques.¹⁹ A recent longitudinal study used a single question to assess memory complaints with an average follow-up of 3.2 years and found that subjective memory complaint was a relatively strong predictor of incident Alzheimer's disease in older persons in whom cognitive impairment was not yet apparent.²⁰ In a review of clinical and population-based studies, Jonker et al.²¹ reported an association between memory complaints and memory impairment in elderly subjects, after adjustment for depressive symptomatology.

In several community-based studies, subjective memory complaint has been found to be associated with depression symptoms,^{22,23} and in the MIRAGE data set (the same data set utilized for this study), depression symptoms occurring even 25 years prior to dementia were associated with an increased risk of developing Alzheimer's disease.¹⁵ These reports suggest that depression symptoms cannot only be part of the preclinical phase of Alzheimer's disease, but may also be an early risk factor for later development of Alzheimer's disease.

Our participants were only evaluated at one point in time; thus, we cannot comment on the predictive value of subjective memory complaint. However, we have shown two significant associations with subjective memory complaint among relatives of patients with Alzheimer's disease. Consistent with some of the cross-sectional studies above, subjective memory complaint among cognitively healthy relatives of Alzheimer's disease patients was associated with a prior history of depression symptoms. Since memory complaint (with or without memory impairment) is a common symptom of depression,^{24,25} this suggests that subjective memory complaint in the presence of healthy cognition should trigger an evaluation for depression.

Subjective memory complaint was also more common among first-degree biological relatives of Alzheimer's

TABLE 1. Sample Characteristic, by Response to the Memory Complaint Question

Characteristic	Subjective Memory Complaint	
	Yes (N = 134)	No (N = 1,365)
Mean Age (SD)	69.6 (10.5)	68.4 (10.1)
Sex		
Male (%)	44 (32.8)	530 (38.8)
Female (%)	90 (67.2)	835 (61.2)
Ethnicity		
African-American (%)	14 (10.4)	251 (18.4)
Caucasian (%)	110 (82.1)	1,051 (77.0)
Other (%)	10 (7.5)	63 (4.6)
Education ≤ 12 years (%)	98 (73.1)	985 (72.2)
Relationship to Proband		
1 Relative* (%)	101 (75.4)	1,102 (80.7)
Spouse (%)	33 (24.6)	263 (19.3)
History of Depression Symptoms (%)	28 (20.9)	97 (7.1)
History of Diabetes (%)	15 (11.2)	131 (9.6)
History of Heart Disease (%)	30 (22.4)	246 (18.0)

*Including parents, siblings, and children

TABLE 2. Predictors of Subjective Memory Complaint

Predictor	Adjusted Odds Ratio* (95% CI)
First-Degree Relative [†] of Proband	1.9 [‡] (1.3, 3.0)
History of Depression Symptoms	3.5 (2.1, 5.7)
History of Diabetes	1.4 (0.79, 2.5)
History of Heart Disease	1.3 (0.82, 1.9)

*Adjusted for age, sex, ethnicity, and education as well as the variables cited above
[†]Including parents, siblings, and children
[‡]Compared with spouses

disease patients than among their spouses. The interpretation of this is unclear. One explanation is that since biological relatives of Alzheimer's disease patients are at higher risk of developing Alzheimer's disease than are spouses of Alzheimer's disease patients,⁷ the higher proportion of subjective memory complaint could reflect the sub-clinical manifestation of Alzheimer's disease. Alternatively, since Alzheimer's disease is now widely recognized as having a heritable component,^{7,26} biological relatives may be more sensitized to memory lapses than spouses and may report them more frequently.

Our study is limited by the cross-sectional nature of the data collection, as noted above. Cognitive testing to confirm self-report of normal cognition was only available in a subset of the participants; however, the correlation between self-report and telephone cognitive testing was very high. The use of a single-item, self-reported measure to examine a complex construct, such as depression, may not be accurate enough to avoid misclassifications. Moreover, we have emphasized that we assessed "depression symptoms" rather than depression. Nonetheless, previous research on depression screening has found that a two-item measure,²⁷ or even a single question,²⁸ can be an effective screen for depression. In our study, relatively few participants endorsed subjective

memory complaint compared with population prevalence studies that have reported a prevalence of 25% or more.²⁹ Self-selection may have resulted in a healthier sample with fewer complaints of memory problems than in the general population. However, to our knowledge this is the first study to examine the predictors of subjective memory complaints in cognitively healthy relatives of Alzheimer's disease patients. Longitudinal studies of relatives are needed to define the association between subjective memory complaint and Alzheimer's disease in this at-risk population.

Based on what is known about the predictors of subjective memory complaints among cognitively healthy relatives of patients with Alzheimer's disease, when family members present such complaints, clinicians should evaluate them for memory impairment, since memory complaints may herald the onset of Alzheimer's disease. If objective memory testing reveals no impairment, then depression should be considered as an alternative explanation for the complaint.

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