Patient Age Influences Recognition of Alzheimer’s Disease

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Background. This study evaluated whether patient age influences recognition of Alzheimer’s disease (AD) as assessed by referrals to a specialty clinic.

Methods. The age and Mini-Mental State Exam (MMSE) at the initial visit to a memory loss clinic of all patients with a diagnosis of AD (n = 533; 88.7%) or amnestic Mild Cognitive Impairment (n = 68; 11.3%) seen from 1992 through 2004 were examined. Only patients seen at least twice were considered so that the potentially confounding effects of age on rate of decline could be examined.

Results. There was a significant inverse correlation between age and MMSE score at initial visit (Spearman rho = −0.10, p = .016). Mixed-model regression analyses revealed significant effects of age and calendar year at initial visit on initial MMSE score and estimated the annual rate of decline on the MMSE at 1.58 points per year. Age at initial visit was not related to the rate of MMSE decline over time.

Conclusions. Recognition of symptoms of AD is delayed as patients age. This delay is not explained by a difference in the rate of decline with age. Even though AD incidence increases dramatically with age, older patients were found to be more advanced in their disease at the time of referral to a dementia clinic.

Key Words: Alzheimer’s disease—Dementia—Age—Diagnosis—Progression—Mini-Mental State Exam—Mild Cognitive Impairment—Dementia clinic.

ALZHEIMER’S disease (AD) is the leading cause of dementia worldwide (1) and the main contributor to the steep increase of dementia prevalence with age (2). Age bias in medical referral and treatment for a variety of conditions is well documented, resulting in less aggressive diagnostic workup and treatment for older adults (3–7). The present study examines whether patient age is related to degree of cognitive impairment at initial presentation to a specialty memory clinic and to rate of cognitive decline in AD. The change in referral patterns over time also is examined by comparing the average age and Mini-Mental State Exam (MMSE) at the initial visit between calendar years.

The rate of decline in AD may influence when symptoms are recognized and when patients are referred to specialty clinics. At some point, change in symptoms surpasses the threshold of “within normal limits,” and this threshold may have as much to do with the rate of change as the development of any particular symptom. There is great variability in the course of cognitive decline in AD (8–11), and numerous variables have been examined as predictors. However, few predictors of decline have produced consistent results. A meta-analysis including data from 37 studies (total sample size = 3492) tracking cognitive decline in AD failed to find any population characteristic that accounted for a significant proportion of variance in the rate of decline (9).

In the present study, rate of decline was considered the major potential confounder in the determination of the effects of age on the timing of initial referral to a specialty memory loss clinic. Older age has been associated with increased (12,13), decreased (14–17), or no effect (18,19) on the rate of cognitive decline in AD. Notably, the literature does not offer any evidence that increasing age is associated with a more benign course of AD. Mixed-effects linear regression models (20) were fitted for MMSE data obtained at initial and multiple follow-up visits in the sample presented. The conclusions presented, therefore, consider the potential confounding effects of rate of decline when determining whether age affects the timing of patient referral for an evaluation of AD.

METHODS

Setting

The Geriatric Research, Education and Clinical Center (GRECC) Memory Loss Clinic at the Minneapolis, Minnesota, Veterans Affairs Medical Center (VAMC) is an interdisciplinary clinic specializing in the evaluation of cognitive disorders in elderly persons.

Participants

Study participants consisted of all patients seen in the GRECC Memory Loss Clinic between January 1992 and December 2004 who completed the MMSE (21) on at least two occasions, and had received a diagnosis of possible or probable AD (22) or the amnestic form of Mild Cognitive Impairment (MCI) (23) at their most recent clinic visit. Amnestic MCI was included in the analysis because such patients frequently go on to develop AD, and the goal was to assess at what stage (how early) in the dementia process patients are referred for evaluation. Data from all participants were part of a database approved by the institutional review board at the Minneapolis VAMC.
Measures

Cognitive decline was assessed using the MMSE (21). The MMSE is the most frequently used clinical tool to screen for and monitor progression in AD. The vast majority of published research on cognitive decline in AD reports MMSE scores, and its use allows for direct comparison with results from an extensive body of literature. Although the MMSE may be relatively insensitive to the presence of early AD (24) or to changes in more advanced AD over <3 years (25), it succinctly communicates information about the relative severity of dementia and is useful in assessing disease progression in groups of patients (9). Additionally, the present sample consists mostly of patients with moderate impairment (mean initial MMSE = 19.9), which should minimize such floor and ceiling effects (26). The MMSE has good test–retest reliability with AD patients (ranging from .74 to .94), as well as moderate-to-high correlations with other cognitive screening instruments and measures of disease progression (see 26 for review).

Data Analysis

The relationship between age and initial MMSE was calculated using a Spearman rho rank order correlation coefficient. Mixed effects (hierarchical) linear regression models were used to examine the effects of age and calendar year on initial visit MMSE and the effect of age on the rate of decline over time in the MMSE. Mixed-effects models have proven an effective tool for assessing rate of cognitive change in AD (11,13,27). Analyses were performed using SPSS version 14 (SPSS Inc., Chicago, IL).

RESULTS

Of 901 patients identified, 601 (66.7%) had possible or probable AD or amnestic MCI. Five hundred thirty-three patients (88.7%) were diagnosed as possible or probable AD, and 68 (11.3%) had a primary diagnosis of amnestic MCI. Patients with possible or probable AD and amnestic MCI were combined for the analyses. The mean age at initial presentation was 76.05 years old (standard deviation [SD] = 6.37; range = 51.70–93.04); 580 (96.5%) were men; 177 (29.5%) had two data points (MMSE scores), 147 (24.5%) had three data points, and 277 (46%) had four or more data points (range = 4–10). The average interval between initial and most recent MMSE was 2 years (range = 1 month–9 years), and 92% were separated by at least 6 months. The mean initial MMSE was 19.9 (SD = 6.4).

A significant correlation was found between age and MMSE at initial visit (Spearman rho = −0.10, p = .016; see Figure 1). Older patients had significantly lower MMSE scores at their initial visit than did younger patients.

One hundred seventeen patients (19.5%) had an initial MMSE score ≥26. A significantly smaller proportion of older (over the median age of 76.7 years) versus younger patients had an MMSE score ≥26 (15.2% vs 23.9%; p = .007), further indicating that not only were older patients more impaired on average when initially seen, but also they were significantly less likely to be identified in the early stages of AD.

The average initial MMSE of new patients with possible or probable AD or MCI rose significantly over time (calendar year vs initial MMSE, Spearman rho = 0.20, p < .001, n = 595; data on six patients seen prior to 1992 not included). Patients had a mean initial MMSE score of 15.6 (SD = 8.1) in 1992 and 20.1 (SD = 6.6) in 2004. Average patient age also increased significantly over time (Spearman rho = 0.11, p = .008, n = 595), starting with a mean of 75.6 (SD = 6.1) in 1992 and ending with a mean of 78.1 (SD = 5.3) in 2004.

The unadjusted mixed-effects model estimate of initial visit MMSE score was 20.14 (standard error [SE] = 0.26), and the estimated annual rate of MMSE decline (slope) for the entire group was 1.68 (SE = 0.10) points per year. The adjusted mixed-effects model included age at initial visit and calendar year of initial visit, and it assessed for whether rate of decline was affected by age at initial presentation. MMSE at initial visit was significantly related to age at initial visit (p = .011) and to calendar year of initial visit (p < .001). MMSE at initial visit was estimated to be 0.10 (SE = 0.04) points lower for each additional year of age. Initial visit MMSE was estimated to increase 0.32 (SE = 0.07) points for each successive calendar year of initial visit. The rate of decline in the MMSE was unrelated to age at initial presentation (Age × Time interaction, p = .98). The estimate of the rate of MMSE decline in the presence of these adjustment covariates was 1.58 (SE = 0.12) points per year.

DISCUSSION

The present study examined the relationship between patient age and the recognition of symptoms of AD as assessed by referrals to a dementia clinic. There was a significant correlation between increasing age and decreasing MMSE score at initial visit. Older patients were
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significantly less likely to be identified early in the course of disease (higher MMSE). No relationship was found between age and rate of decline on the MMSE. The present study’s adjusted linear annual rate of change of 1.58 MMSE points per year is consistent with previously reported rates and falls within the range reported by a recent meta-analysis (0.9–5.7) (9). Based on the mixed-model regression analysis of our clinic data, the MMSE at initial visit is quite discrepant for younger and older patients. For example, a 65-year-old patient entering our clinic has an estimated initial visit MMSE of 21.14 versus 19.10 for an 85-year-old patient, a difference of two MMSE points. Based on our estimated annual rate of MMSE decline (1.58 MMSE points per year, covariate-adjusted model), the two-point difference in initial visit MMSE for these two patients translates into a 16-month delay in the recognition of disease in the older patient.

Given that the average rate of decline on the MMSE in AD is independent of age, it is concerning that older patients were referred for evaluation later in the disease course than were younger patients. As the incidence of dementia increases with age, vigilance in assessing for dementia should also increase, and patients should be identified earlier in the course of AD. However, AD usually is identified only after symptoms are obvious, as revealed by the mean initial MMSE of 19.9 in the present study. That older patients are identified later in the disease course, despite the marked age-related increase in AD, suggests that clinicians do not attach the same significance to symptoms of dementia in older patients compared to younger ones. There are several possible explanations for this phenomenon. Older patients have more comorbid diseases, the care of which may overshadow the assessment for possible dementia. Competition for medical resources may focus clinician attention on conditions perceived to be more treatable. Furthermore, comorbid conditions may be misinterpreted as a cause of cognitive impairment, and the recognition of a progressive dementia may be delayed as other problems are addressed. Finally, clinicians, like patients and families, may have an ageist bias, believing that early symptoms of dementia are a “normal” part of aging, rather than a reflection of age-related disease. Ironically, the failure to recognize and treat dementia symptoms, even in the oldest patients, complicates the management of other medical conditions (e.g., 28,29).

Although it may be argued that the average MMSE in normal older adults declines (30), the average initial MMSE of 19.9 in the patient population presented is unambiguously in the impaired range. The delay in recognition of AD eventually may have an adverse effect on efforts aimed at slowing or reversing the earliest pathophysiological changes in the disease. Because the disease progresses at similar rates regardless of age, the underlying pathophysiology is likely to be similar, and all patients eventually may benefit from such treatment. Even in the absence of a cure, early recognition of AD is important to allow patients and families the time needed to plan for this life-altering disease.

We did not address the functional abilities of our patients in this analysis. Functional deficits certainly could influence when patients are identified as cognitively impaired. Younger patients still in the work force may be identified earlier in the course of AD as problems on the job are often the first functional deficits to appear. Conversely, among retired patients, older adults with more comorbid illnesses (e.g., deficits in vision, hearing, and mobility) may be less able to compensate for cognitive deficits than their younger, healthier counterparts, and symptoms of AD may appear at an earlier stage. Given the average age (76.05 ± 6.37) of our study population, it is unlikely that poor job performance led to a significant number of referrals. Still, the question of the effects of functional deficits cannot be answered by our analysis.

Limitations of the present study include its retrospective design and the patient population (veterans, 96.5% male, from the upper Midwest, referred to a dementia specialty clinic), which may limit the generalizability of the results. Strengths of the study include a large sample and the setting of a well-established dementia clinic, the Minneapolis VAMC GRECC Memory Loss Clinic. The attending physician staff remained largely unchanged over the years reviewed, providing a consistent assessment of patients. The administration of the MMSE was standardized (31). The source of patients and the referral patterns also did not change appreciably over the years reviewed, further supporting the validity of the comparisons made.

Summary

The data presented show that older age is associated with more advanced dementia at the time of referral to a specialty clinic. The rate of cognitive decline in AD was found to be independent of age and cannot explain the delay in referring older patients. In general, patients are referred for evaluation only after the disease is moderately advanced. Clinicians need to be more attuned to the early recognition of AD, particularly in their oldest, most at-risk patients.

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