The Effects of Age on Rate of Progression of Alzheimer Disease and Dementia With Associated Cerebrovascular Disease

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Background: Relatively little is known about how cerebrovascular disease affects progression of dementia. Previous studies have found no differences in progression of Alzheimer disease and vascular dementia, but these studies have not specifically examined age effects.

Objective: To test whether the rate of cognitive decline is different in Alzheimer disease compared with dementia with associated cerebrovascular disease in clinical and autopsy patient series.

Patients and Methods: We studied the longitudinal course of cognitive function as measured by the Mini-Mental State Examination (MMSE) in patients with clinically and neuropathologically diagnosed conditions evaluated through a university Alzheimer disease center. Clinical patients were grouped according to possible Alzheimer disease without stroke (n=37), probable Alzheimer disease without stroke (n=181), and dementia with stroke (n=50). Autopsy cases were categorized into Alzheimer disease (n=78) and dementia with vascular disease (n=13). Data were analyzed using random-effects modeling of longitudinal change.

Results: There was a significant interaction between age and diagnosis in determining rate of change on the MMSE scores for both the clinical and autopsy samples. Rate of change decreased slightly with advancing age for Alzheimer disease groups, but increased with age for dementia with cerebrovascular disease groups.

Conclusions: Dementia with cerebrovascular disease declined faster in patients 80 years and older compared with Alzheimer disease without associated cerebrovascular pathological conditions, but showed slower decline in patients younger than 80 years. This effect most likely reflects combined Alzheimer and vascular pathological conditions in older patients with cerebrovascular disease.

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Factors influencing the rate of decline of patients with Alzheimer disease (AD) have been examined in a number of studies. Factors that have been frequently associated with more rapid decline include more severe dementia,\(^1,4\) earlier age at onset,\(^5,6\) extrapyramidal signs,\(^7-10\) language impairment,\(^10-16\) and psychiatric symptoms.\(^8,10,17,18\) In neuropathologically examined cases, the presence of Lewy bodies in addition to pathological changes of AD have been associated with more rapid decline.\(^19\) In contrast, relatively little is known about the rate of progression of patients with vascular dementia (VaD). Although a few studies have reported similar rates of decline for VaD and AD\(^20,21\) and for mixed AD and VaD,\(^22\) little is known about the progression of VaD or about the interaction between cerebrovascular disease and AD in determining progression of dementia.

Diagnostic uncertainty associated with VaD presents major limitations for both clinical practice and research. Even though cerebrovascular changes can be reliably identified using modern imaging techniques, presence of AD changes cannot be ruled out for patients who meet clinical criteria for diagnosis of VaD. Because of these problems, some have recommended an alternative, descriptive approach to classification in which dementia with and without stroke are classified separately,\(^23-25\) making no assumptions about the extent of contribution of different pathological conditions for the dementia. Problems with accuracy of clinical diagnosis highlight the importance of pathological verification of clinical diagnoses.

The purpose of this report was to examine how AD and cerebrovascular disease influence the rate of cognitive decline in patients with dementia. Two independent samples, one defined by clinical diagnosis and the other by pathological diagnosis, were used to examine the rate of decline in patients with AD and in patients with dementia with cerebrovascular disease.
SUBJECTS AND METHODS

SUBJECTS

Two nonoverlapping samples of subjects who had undergone clinical evaluation and longitudinal follow-up were used in this study: a clinical sample composed of 268 patients and an autopsy sample of 91. All patients of a university dementia program were given a comprehensive diagnostic workup under a standardized protocol that included a neurological examination, brain scan, neuropsychological examination, and appropriate laboratory analyses.

CLINICAL SAMPLE

The clinical sample included patients with a clinical diagnosis of probable or possible AD, probable or possible ischemic vascular dementia (IVD), or mixed (AD/IVD) dementia.

Participants were first classified according to the presence vs absence of stroke. Those without stroke were then classified as having possible or probable AD, yielding 3 groups: (1) possible AD without stroke (ADPo) (n = 37), (2) probable AD without stroke (ADPr) (n = 181), and (3) dementia with stroke (DS) (n = 50). Presence of stroke was based on a reading of a brain imaging study (computed tomography, n = 139; magnetic resonance imaging, n = 129) by the examining neurologist. The DS group contained 17 (34%) patients with a clinical diagnosis of probable IVD, 3 (6%) with possible IVD, 19 (38%) with mixed AD/IVD, 8 (16%) with possible AD, and 3 (6%) with probable AD. The stroke was judged by the examining clinicians to not be etiologically related to the dementia in the probable AD cases. Subcortical stroke was present in 39 (78%) patients, 8 patients (16%) had cortical stroke, and 3 (6%) had both subcortical and cortical stroke.

Demographic characteristics and baseline cognitive functioning of the clinical sample are presented in Table 1. Groups were compared using a 1-way analysis of variance for continuous variables and a χ² test for the dichotomous variable of sex. Groups were well matched for demographic characteristics and degree of cognitive impairment at baseline evaluation.

There were 735 observations for the 268 clinical sample participants. Scores from 2 assessments were available for 148 patients (53.2%), and there were 3 assessments for 68 patients (25.4%) and 4 or more for 52 patients (19.4%). Distribution of number of follow-ups did not significantly differ across groups using the χ² test (P > .50). Average time from first to last assessment was 2.15 years (SD, 1.23 years; range, 0.39-6.02 years). A 1-way analysis of variance showed that groups significantly differed in length of follow-up (P < .04; mean ADPo follow-up, 1.82 years; ADPr follow-up, 2.28 years; DS follow-up, 1.89 years). One hundred twenty-nine (48.1%) of the 268 cases were in active follow-up at the time of this report, 43 (16.0%) had died, 17 (6.3%) had refused or were lost to follow-up, and 80 (29.9%) were dropped from further follow-up because they did not meet the overall scientific goals of the program.

AUTOPSY SAMPLE

The autopsy sample consisted of 91 patients with a final pathological dementia diagnosis of either AD or cerebrovascular disease (VaD). As for the clinical sample, these subjects were assigned to groups according to the presence or absence of cerebrovascular disease as determined by pathological examination of the brain. One group (ADpath, n = 78) consisted of 73 patients (94%) with a primary pathological diagnosis of definite AD according to Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) neuropathological criteria and 5 patients (6%) with CERAD probable AD. These patients had no other identified pathological cause of dementia, and consequently, this is a group defined by “pure” AD pathology. A second group (DS path, n = 13) included patients with a primary or secondary pathological diagnosis of cerebrovascular disease. Nine (69%) had a primary diagnosis of definite AD and a secondary diagnosis of VaD, 2 (15%) had primary probable AD with secondary VaD, 1 (8%) had primary VaD and secondary possible AD, and 1 (8%) had primary VaD and secondary limbic sclerosis. The initial clinical diagnosis for the ADpath group was predominantly AD: probable AD (n = 42, 54%), possible AD (n = 19, 24%), and mixed dementia (n = 7, 9%). In the DS path group, 7 (54%) had mixed AD/IVD, 4 (31%) had probable AD, 1 (8%) had possible AD, and 1 (8%) had other dementia.

Demographic information for the autopsy sample is presented in Table 2. Age at baseline was significantly younger in the AD group, but the groups did not significantly differ with respect to sex, education, or baseline cognitive functioning.

RESULTS

CLINICAL SAMPLE

Rate of change on the MMSE score was significantly predicted only by the age × diagnosis interaction effect (F2,198 = 4.24, P < .02) (Figure 1). This figure shows average rate of change predicted by the random-effects model for the 3 groups at different ages from 65 to 85 years. Predicted rate of decline for the ADpo group decreased from about 3.5 MMSE points per year at the age of 65 years to less than 1.5 points at the age of 85 years. Predicted rate of decline for the ADpr group was greater for younger (3.1 points at 65 years) than for older age at baseline (1.9 points at 85 years). Predicted rate of change in the DS group increased with age (1.5 points at 65 years vs 2.8 points at 85 years). Predicted rate of decline for the DS group was less than for both AD groups until about the age of 80 years and was greater for those 80 years and older. Results were unchanged when only patients who are currently in active follow-up were used and in the secondary analysis of the rate-of-change measure.

It is possible that the faster rate of cognitive decline in older patients in the DS group was due to greater severity of cerebrovascular disease or greater medical comorbidity. To address this hypothesis, subjects in the DS group who were younger than 80 years (n = 29) were compared with those 80 years and older (n = 21). Extent of cerebrovascular disease was operationally defined in 2 ways: a clinical judgment at the time of initial diagnosis of the extent...
There were 244 observations for the 91 autopsy sample subjects. Scores from 2 assessments were available for 48 patients (53%) from this sample, while there were 3 assessments for 29 (32%) and 4 or more for 14 (15%) patients. Distribution of number of follow-ups did not significantly differ across groups (P > .11). Average time from first to last assessment was 2.14 years (SD, 1.20 years; range, 0.42-6.27 years). Length of follow-up did not significantly differ across groups (P > .91).

NEUROPATHOLOGY METHODS

Brains removed at autopsy were fixed in 10% neutral-buffered formalin solutions for at least 10 days, and cerebral hemispheres were coronally sectioned at 5- to 7-mm intervals. Sections were inspected by the naked eye and with a hand lens. Each section then was photographed, and photographs were inspected for infarcts and compared with imaging studies. Multiple tissue blocks were taken from most cortical, subcortical, brainstem, and cerebellar regions, with special emphasis on areas suspected to be abnormal in imaging studies. Blocks were embedded in paraffin and 10-µm-thick sections stained with hematoxylin-eosin; most blocks were stained with the Bielschowsky modified silver technique. Selected peryvertricular white matter zones and all infarcted or focally atrophic regions were stained with Luxol fast blue cresyl violet and glial fibrillary acidic protein antibody stain (monoclonal, 1:1000; Dako, Carpinteria, Calif). Selected cortical and brainstem blocks were stained by immunohistochemistry with antibodies against tau 2 (monoclonal, 1:100; Novocastra, Newcastle upon Tyne, England), Alz50 (1:100; Peter Davies, MD, Bronx, NY), β-amyloid (monoclonal, site 8-17, 1:100; Novocastra), ubiquitin (monoclonal, 1:1000; Novocastra), and α-synuclein (monoclonal, 1:25; Novocastra, or polyclonal, 1:200; Santa Cruz Biotechnology, Santa Cruz, Calif). Antibody binding was detected by the avidin-biotin method using 3,3'-diaminobenzidine chromogen.

DESIGN

Longitudinal change in cognitive functioning was measured with the Mini-Mental State Examination (MMSE).29 Variables used to predict change in the MMSE scores included demographic variables (sex, age at initial evaluation, and education) and diagnostic group (ADpo, ADpr, and DS in the clinical sample; ADpath and DSpath in the autopsy sample). In addition, an age × group interaction effect was included to test whether age-moderated effects were related to diagnosis. Data were censored to address potential problems associated with floor and ceiling effects of the MMSE by excluding records with MMSE scores higher than 25 or lower than 5. Also, initial evaluations with MMSE scores below 10 were excluded. The MMSE scores were constrained to 5 to 25 because a previous study has shown linear measurement characteristics within that range.30 Initial scores below 10 were excluded because, with a cutoff of 5 in effect, cases beginning below that level had insufficient range in which to decline.

DATA ANALYSIS

Data were analyzed using a mixed-model, random-effects regression analysis to model change in the MMSE and identify predictors of change.31,32 This analysis, performed with SAS Proc Mixed software (SAS Institute Inc, Cary, NC), incorporated random-effects terms to account for subject and subject × time differences in the MMSE scores. Terms were included to account for effects on initial MMSE scores of age, education, sex, and diagnostic group. Terms to account for longitudinal change in the MMSE scores included sex, age, education, and diagnostic group. In addition, a term was incorporated into the model to assess interactive effects of age and diagnostic group. Random-effects models are sensitive to assumptions that random effects are linear and normally distributed. These assumptions were examined using graphical diagnostics. Residuals were examined to ensure that they were normally distributed, and plots of residuals against predicted values and effects were examined to verify that non-linear trends in the data were not present. Additional diagnostics included evaluation of variance components related to random effects and within-subject error variance to address adequacy of statistical estimation procedures associated with the random-effects modeling.

A secondary analysis of longitudinal effects was performed using more traditional methods applied to a rate-of-change score defined by the last MMSE score minus the first divided by the time, in years, between these 2 assessments. This change score was then entered as a dependent variable into a general linear model in which sex, gender, education, diagnostic group, and the age × diagnostic group interaction were included as independent variables.

AUTOPSY SAMPLE

Rate of change of the MMSE scores was significantly predicted only by the age × diagnosis interaction effect (F1,62 = 5.47, P < .03) (Figure 2). Predicted decline for the DSpath group is constrained to the 75- to 85-year range in Figure 2, since the age range of participants in this group extended from 73 to 89 years, making extrapolation to ages younger than 75 years problematic. Predicted rate of decline for the ADpath group decreased from 3.8 MMSE points per year at the age of 65 years to 2.8 points at the age of 85 years. Predicted rate of change for the DSpath group changed from 1.6 MMSE points per year at the age of 75 years to 4.3 points per year at the age of 85 years.

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Rates of decline for the ADpath and DSpath groups were essentially the same at the age of 80 years, but decline was greater for the DSpath group at ages older than 80 years. Again, results from the secondary analysis of the derived rate of change measure were the same.

For the ADpath group, 54 (96%) of 56 patients younger than 80 years had a primary pathological diagnosis of CERAD-definite AD, and 19 (86%) of 22 in the 80 years or older category had a primary pathological diagnosis of definite AD. For the DSpath group, 2 (40%) of 5 patients younger than 80 years had definite AD, but 7 (88%) of 8 in the 80 years or older group had definite AD. This indicates a lesser degree of AD pathology in the younger patients in the DSpath group compared with the older DSpath patients.

Table 1. Demographic Characteristics of Clinical Sample Participants by Group*  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Possible AD (n = 38)</th>
<th>Probable AD (n = 181)</th>
<th>Dementia With Stroke (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education, mean (SD), y</td>
<td>12.3 (3.9)</td>
<td>12.8 (3.4)</td>
<td>11.5 (3.9)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>77.2 (7.2)</td>
<td>74.9 (8.7)</td>
<td>77.6 (8.0)</td>
</tr>
<tr>
<td>Baseline MMSE score, mean (SD)</td>
<td>19.6 (4.3)</td>
<td>19.5 (3.9)</td>
<td>20.0 (3.3)</td>
</tr>
<tr>
<td>Sex, M/F, %</td>
<td>43/57</td>
<td>29/71</td>
<td>32/68</td>
</tr>
</tbody>
</table>

*Groups did not significantly differ (P > .05) on any variable. AD indicates Alzheimer disease; MMSE, Mini-Mental State Examination.

Table 2. Demographic Characteristics of Autopsy Sample Participants by Group*  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AD (n = 78)</th>
<th>Dementia and Stroke (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education, mean (SD), y</td>
<td>13.4 (3.1)</td>
<td>12.1 (4.1)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>74.2 (8.2)</td>
<td>81.2 (4.5)</td>
</tr>
<tr>
<td>Baseline MMSE score, mean (SD)</td>
<td>18.8 (4.3)</td>
<td>18.2 (3.2)</td>
</tr>
<tr>
<td>Sex, M/F, %</td>
<td>33/67</td>
<td>46/54</td>
</tr>
</tbody>
</table>

*Groups significantly differed in age at baseline evaluation (P < .004) but not on other variables (P > .15). AD indicates Alzheimer disease; MMSE, Mini-Mental State Examination.

Figure 1. Predicted rate of decline for clinical sample diagnostic groups across the 65- to 85-year age range. Values represent the annual rate of decline in the Mini-Mental State Examination (MMSE) score that is predicted by the random-effects modeling of longitudinal change. ADpath indicates pathologically verified Alzheimer disease (other causes excluded); DSpath, pathologically verified stroke (other causes included).

Figure 2. Predicted rate of decline for autopsy sample diagnostic groups across the 65- to 85-year age range. Values represent the annual rate of decline in the Mini-Mental State Examination (MMSE) score that is predicted by the random-effects modeling of longitudinal change. ADpath indicates pathologically verified Alzheimer disease (other causes excluded); DSpath, pathologically verified stroke (other causes included).

The primary finding in this study was that age, AD, and cerebrovascular disease interact in determining the rate of progression of cognitive impairment. Rate of decline decreased slightly with advancing age for patients with AD uncomplicated by cerebrovascular disease, but increased with age for patients with dementia and cerebrovascular disease. Rate of decline in patients with AD was greater than in those with dementia with vascular disease until about the age of 80 years, but the pattern reversed after the age of 80 years. The strength of this finding is underscored by the fact that it was replicated in the independent clinical and autopsy samples.

Previous literature examining interactive effects of AD and cerebrovascular disease on cognitive functioning helps to explain the obtained results. Both the Nun Study33 and work by Tomlinson and colleagues34 have reported mutually enhancing effects of concomitant AD and stroke on degree of dementia. The effect of age on rate of decline in patients with cerebrovascular disease in this study may reflect a differential load, or likelihood, of Alzheimer pathology at different ages. Thus, younger patients with vascular disease would be more likely to have “pure” vascular dementia, whereas the older cases would be more likely to have 2 pathological processes and consequently to decline more rapidly.

The number of pathologically examined patients with vascular disease was small, especially for those younger than 80 years, but results were consistent with this postulated increase of AD in older dementia patients with vascular disease. All but 1 of the older patients with vascular disease had sufficient AD pathological findings to meet CERAD diagnostic criteria for definite AD, as did more than 95% of the younger and 83% of the older AD patients. In contrast, only 40% of the younger patients with vascular disease met CERAD criteria for definite AD. There did not appear to be age-related differences in severity of cerebrovascular disease or in medical comorbidity that could account for the age effects.

Previous studies examining rate of cognitive decline in dementia35–32 have not found statistically signifi-
cant differences between patients with AD and VaD or mixed dementia. Results of this study are consistent with previous studies when considering overall rate of decline. However, none of the previous studies tested for age x diagnosis interactions in rate of progression, and the conclusion from this study would have been that AD and dementia with cerebrovascular disease do not substantially differ in rate of change if this interaction effect had not been directly tested.

Several methodological issues merit discussion. First, effects of dropouts must be considered. If dropouts are related to factors being used to predict change, inferences about these factors might be biased. The obtained finding that older and younger patients were equally likely to be in active follow-up argues against bias associated with differential dropout. Results related to overall rate of change in this study are generally consistent with other literature, and the age x diagnosis interaction effect was replicated across independent samples, which argue in favor of the validity of the obtained results.

Second, alternative explanations for the observed age effects cannot be excluded. Differential use of cholinesterase inhibitors, for example, could have affected rate of cognitive decline. Third, participants came from a university Alzheimer program, and results may not be representative for patients from the community at large. For example, it is possible that this sample contains a greater proportion of cases with AD pathology than would be found more generally. Finally, the effects of effects of data censoring to restrict MMSE scores to the range of linear measurement must also be considered. As a result of this aspect of the study design, change at very early stages of dementia for high-functioning individuals cannot be addressed, and applicability to more severe levels of impairment is also limited. The MMSE likely is not an optimal measure for longitudinal research in dementia, and other measures may prove to be more effective.

Results of this study indicate that age is an important factor affecting how AD and cerebrovascular disease affect the clinical course of dementia. Age has long been known to have a powerful effect on the clinical presentation of dementia, and this study highlights the importance of further research to better characterize how AD and cerebrovascular disease interact in causing dementia.

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