Small Concomitant Vascular Lesions Do Not Influence Rates of Cognitive Decline in Patients With Alzheimer Disease

Jae-Hong Lee, MD; John M. Olichney, MD; Lawrence A. Hansen, MD; C. Richard Hofstetter, PhD; Leon J. Thal, MD

Objective: To determine the relation between concomitant small cerebral infarction and clinical progression of Alzheimer disease (AD).

Design: A retrospective clinicopathologic study of patients with AD.

Methods: We searched the databases of the University of California, San Diego, Alzheimer's Disease Research Center, La Jolla, for patients with an autopsy diagnosis of definite AD with or without a concomitant small cerebral infarction. Clinical and neuropsychologic data obtained during longitudinal follow-up were available for 201 subjects with AD neuropathologic features and 36 with AD and concomitant cerebral infarcts (volume, <10 cm³). The rates of cognitive decline on the Mini-Mental State Examination and the Dementia Rating Scale were each calculated and compared between the 2 groups.

Results: The age at death was significantly (P = .05) higher and the Braak stage was lower in patients with mixed AD and infarct pathological features compared with those with AD pathological features only. The rate of cognitive decline over time was not significantly (P = .20 for all) different between the 2 groups. There was a trend for the presence of a cerebral infarct to be associated with more severe clinical dementia (P = .08) as measured by the Dementia Rating Scale, but no such trend for the Mini-Mental State Examination.

Conclusion: This clinicopathologic correlation study suggests that concomitant small cerebral infarcts with a total volume of less than 10 cm³ do not significantly influence the overall rate of global cognitive decline in patients with AD.

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Patients with Alzheimer disease (AD) frequently have other concomitant pathological lesions. Since strokes are common in elderly patients and increase with age, in most clinicopathologic series of patients with dementia, 18% to 34% will have AD and infarcts. The contribution of minor degrees of vascular disease to the expression of clinical dementia in patients with AD remains unclear. In a comparative study of AD, vascular dementia, and mixed dementia, memory was more severely involved early in patients with AD. However, memory impairment in those with vascular and mixed dementia eventually caught up with memory impairment in those with AD, suggesting an important role for the ischemic component of mixed dementia. Recent studies suggest that a concomitant cerebral infarction may aggravate the severity of dementia in patients with AD. Infarctions may magnify the effect of mild AD pathological features and result in the earlier expression of dementia. Traditionally, the volume threshold for developing dementia has been considered to be 100 cm³. More recent investigations have considered infarcts with a volume of 10 to 50 cm³ to be significant. However, many previous studies of patients with AD and concomitant vascular pathological features (mixed dementia) have included patients with infarcts of any size. Few studies have examined the contribution of a concomitant infarct with a volume less than 10 cm³, which is generally considered insufficient to produce dementia.

We therefore set out to determine the effect of small, noncritically located infarcts with a volume of less than 10 cm³ on the severity of dementia and the rate of decline of patients with AD in a clinicopathologic study.
SUBJECTS AND METHODS

SUBJECTS

This study included consecutive autopsy specimens from patients with dementia obtained between January 1985 and December 1998 from the University of California, San Diego, Alzheimer’s Disease Research Center, La Jolla. Patients had to meet the following criteria: (1) National Institute on Aging pathological criteria for AD13; and (2) Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, criteria for dementia.14 Patients with other concomitant pathological lesions, such as hemorrhages or diffuse Lewy bodies, on brain autopsy were excluded.

Most patients were followed up longitudinally at the University of California, San Diego, Alzheimer’s Disease Research Center, while the remainder (18%) were examined in a nursing home setting. All Alzheimer’s Disease Research Center subjects underwent at least 1 standardized examination, which includes a medical history, a physical examination, a structured neurologic examination, cognitive screening tests, blood tests, and a neuroimaging study.15 The history regarding the presence or absence of hypertension, diabetes, stroke, and cardiac disease was obtained (annually during follow-up) from an informant (usually the spouse) by either a neurologist or a nurse as part of the medical history. Nursing home subjects were seen by a visiting nurse practitioner from the Alzheimer’s Disease Research Center, who obtained a history and performed the previously described standardized examination. History of stroke was obtained retrospectively at the time of autopsy, by a careful review of all historical data and available medical records. Most subjects (n=201) underwent apolipoprotein E genotyping under the informed consent approved by our institutional review board.

RESULTS

Thirty-six subjects had 1 or more concomitant small infarcts (<10 cm³ in total volume) in addition to AD pathological lesions, and 201 had AD pathological lesions only. The demographic and clinical features are summarized in Table 1. The age at death was significantly higher in the mixed AD group than in the pure AD group. The Braak stage was significantly higher in the pure AD group compared with the mixed AD group. Histories of stroke and hypertension were both more frequent in the mixed AD group than in the pure AD group. There were no group differences in the sex ratio or the severity of cerebral amyloid angiopathy. The frequency of diabetes or cardiac disease did not differ between the groups. The interval between the last examination and death was almost identical. There was no significant intergroup difference in survival after study enrollment. The initial MMSE and DRS scores were similar in the 2 groups. The scores of the MMSE and the DRS at the last examination before death showed nonstatistically significant differences. Apolipoprotein E genotype analysis was conducted to assess the relation of E4 allele frequency with the prevalence of small infarcts. The apolipoprotein E genotype distributions were nearly identical in the mixed and pure AD groups (Table 1). The type and location of infarcts in the mixed AD group are as follows:

<table>
<thead>
<tr>
<th>Infarct Characteristics</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical microinfarcts</td>
<td>18</td>
</tr>
<tr>
<td>Lacunar infarcts</td>
<td>18</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>15</td>
</tr>
<tr>
<td>Subcortical white matter</td>
<td>6</td>
</tr>
<tr>
<td>Thalamus</td>
<td>3</td>
</tr>
<tr>
<td>Multiple infarcts (cortical and subcortical)</td>
<td>6</td>
</tr>
</tbody>
</table>

Cortical microinfarcts and lacunar infarcts were the most common. Most cortical microinfarctions were widespread multiple tiny infarcts (granular atrophy) rather than a single circumscribed cortical infarct. The most frequent location of the lacunar infarcts was the basal ganglia, followed by the subcortical white matter and the thalamus. Combined cortical and subcortical infarcts were found in 6 patients. The association between infarct location and dementia severity was not analyzed because of insufficient sample size.

Since the 2 groups differed considerably in mean age and Braak stage, which could by themselves affect the severity of dementia, we balanced for these variables by eliminating those patients who were younger and who...
amplification technique adapted from Wenham et al, with DNA digestion using the Hhal restriction enzyme and electrophoresis. The detailed methods of this procedure have been reported previously.

NEUROPATHOLOGIC ASSESSMENT

At autopsy, brains were divided sagittally. The left hemibrain was fixed in formaldehyde solution, and the right hemibrain was examined grossly for infarcts or other lesions, then frozen at −70°C for chemical analysis. Following 10 days of formaldehyde solution fixation, the left hemibrain was examined externally and serially sectioned into 1-cm-thick slices in the coronal plane, and evidence of infarction was noted. Tissue blocks were taken from all gross lesions; the midfrontal cortex; the inferior parietal lobe; the superior temporal gyrus; the inferior temporal gyrus; the posterior and anterior cingulate gyrus; the basal ganglia, including the inominate substance and adjacent insula; the mesencephalon; the rostral pons; and the cerebellar vermis. Hematoxylin-eosin–stained preparations from all tissue blocks were prepared for neuropathologic evaluation. These sections sometimes revealed cortical microinfarcts that had escaped gross detection at the time of brain cutting. Senile plaques and neurofibrillary tangles were counted, as previously described. Infarcts were noted and classified by number and site, and the total volume (measured in milliliters) of infarcted brain was estimated.

The severity of cerebral amyloid angiopathy was assessed semiquantitatively on thioflavine S–stained preparations. A score of zero meant no thioflavine S positivity in the leptomeningeal or superficial cortical blood vessels; 1, trace positivity in either the leptomeningeal or cortical blood vessels; 2, at least some vessels in the leptomeninges or neocortex had circumferential brightly staining amyloid deposits; 3, widespread circumferential staining in many leptomeningeal and superficial cortical vessels; and 4, similarly severe amyloid angiopathy was combined with dystrophic changes, ie, thioflavine S positivity emanating from severely amyloid blood vessels into surrounding neuropil. A single cerebral amyloid angiopathy severity score for each subject was calculated by averaging across all of the available regional cerebral amyloid angiopathy scores.

A modified Braak stage based on the distribution of neurofibrillary tangles was used for neuropathologic staging of AD-related changes, which reflects the extent of pathological lesions in brains with AD.

STATISTICAL ANALYSIS

For between-group comparisons, we used the χ² test for categorical dependent variables and the t test for continuous variables. When parametric statistical assumptions were not satisfied, the Mann-Whitney test was applied. To adjust for attrition, differing periods of observation, and varying levels of dementia severity, we used a mixed-model, random-effects analysis in which the rate of progression for each cognitive measure was modeled as a function of level and change in level. Groups were compared with an analysis of covariance, likelihood ratio test for continuations, and likelihood ratio test for categorical dependent variables and the χ² test for continuations. When parametric statistical assumptions were not satisfied, the Mann-Whitney test was applied. To adjust for attrition, differing periods of observation, and varying levels of dementia severity, we used a mixed-model, random-effects analysis in which the rate of progression for each cognitive measure was modeled as a function of level and change in level. Groups were compared with an analysis of covariance, likelihood ratio test for continuations, and likelihood ratio test for categorical dependent variables and the χ² test for continuations.
On the DRS, patients with concomitant infarcts had an annual decline of 16.0 points, while those with pure AD had an annual decline of 17.5 points. Again, there were no statistically significant intergroup differences.

These results show that the severity of dementia in patients with AD was not significantly affected by a concomitant small (<10 cm³ volume) infarct. The suggested volume threshold for an infarct to definitely cause dementia was at least 100 cm³, while infarcts with a volume of less than 100 cm³ variably caused dementia according to Tomlinson et al.9 Recent radiological and pathological studies10,11 have confirmed that many patients with infarcts with a volume between 10 and 50 cm³ had dementia. However, even a small infarct with a volume of less than 10 cm³ is sometimes reported to cause dementia, particularly if it occurs in a strategic area involving cognitive processing.24 The effect of additional pathological lesions, albeit negligible by themselves, might add to the cognitive deficit in patients with AD in an additive or interactive manner. However, we found that small concomitant infarcts (<10 cm³ in volume) neither worsened dementia severity near death nor increased the observed rate of decline. This remained true even when we compared subgroups matched for age and AD pathological severity, although the last DRS score tended to be lower in the mixed group. Others8 have found that mild vascular pathological lesions in patients with AD, such as lacunar infarcts, did not influence the degree of clinical dementia and that a major degree of white matter pathological features or major infarctions was needed for additivity.

Unlike the Nun study6 or the report by Heyman et al.7 we did not find that the presence of small cerebral infarcts significantly affected the severity of clinical dementia, although there was a trend toward the presence of a cerebral infarction being associated with more severe dementia on the DRS. This difference may be due to a difference in the method of patient selection: we defined the ischemic vascular lesion as an infarct with a volume of less than 10 cm³ in contrast to the Nun study, in which lacunar (<1.5 cm) and larger infarcts were included. Brain infarcts of smaller volumes are likely to have less impact on the clinical expression of AD. In the present study, the age at death of the mixed AD group (83.6 years) was significantly higher than that of the pure AD group (79.4 years). This is probably due to the fact that cerebral vascular lesions are found more frequently as patients become older.1,2 On the other hand, the Braak stage of the mixed AD group was significantly lower than that of the pure AD group, suggesting that when additional vascular pathological features are present, the degree of dementia may be similar despite the presence of fewer AD pathological lesions.

Although the apolipoprotein E4 allele has been well demonstrated to increase the risk of premature coronary artery disease and may increase generalized atherosclerosis,25-27 its role in patients with stroke and vascular or mixed dementia is much less clear.28,29 In the present study, it was not associated with the presence of concomitant mild vascular pathological lesions.

We found that the presence of small concomitant infarcts did not alter the rate of cognitive decline. The rate of cognitive decline in patients with AD is highly variable. The average annual change in the MMSE score for a population of patients with AD varied from 1.8 to 6.7 points per year.30 Despite the wide variation in individual annual score changes as a group, the average MMSE score of patients with pure AD declined about 3.2 points per year and the average DRS score declined by 13.2 points per year. These values are consistent with those in other published reports. The study conducted by Salmon et al31 revealed an average annual decline of 2.8 points on the
MMSE and 11.4 points on the DRS and suggested that the DRS, with its greater range, reflects the change with increasing dementia severity more precisely. The apparent disparity in the direction of change between the MMSE and the DRS score at the last examination (higher MMSE and lower DRS score in patients with mixed AD compared with those with pure AD) in the present study may reflect a more precise measurement by the DRS in the later stages of dementia. Also, since the DRS has a higher proportion of tests that measure “frontal” function (ie, attention and initiation/perseveration subscales) rather than memory and orientation relative to the MMSE, it is possible that the somewhat lower DRS scores may indicate a relative preponderance of “frontosubcortical” type deficits in our mixed group.

Random-effects models for longitudinal data analysis are suitable for recognizing the relation between serial observations on the same unit and dealing with highly unbalanced data, which is common with many longitudinal studies. Considerable variation among individuals in the number and timing of measurements, as in this study, caused unbalanced data sets that cannot be analyzed properly using a general multivariate model with an unrestricted covariance structure. In a random-effects model for longitudinal data, the probability distribution for the multiple measurements has the same form for each individual, but the distribution of these variables (random effects) varies among individuals. The slope (rate of annual decline), a random-effects variable calculated in this model, may differ from that obtained by simply calculating the cognitive score difference divided by the interval between testings (ie, \(\frac{[\text{initial MMSE (or DRS) score} - \text{last MMSE (or DRS) score}]}{\text{time}}\)) or by an ordinary least squares regression analysis, but the random-effects model for longitudinal data approach better represents the data provided in the present study.

### Table 3. Annual Scores on the MMSE and the DRS in the Mixed and Pure AD Groups (Preadjustment)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Score, Mean ± SD</th>
<th>At Enrollment</th>
<th>1 y</th>
<th>2 y</th>
<th>3 y</th>
<th>4 y</th>
<th>5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n = 118)</td>
<td>(n = 107)</td>
<td>(n = 80)</td>
<td>(n = 59)</td>
<td>(n = 44)</td>
<td>(n = 30)</td>
</tr>
<tr>
<td>Mixed AD (n = 21)†</td>
<td>MMSE</td>
<td>18.1 ± 7.0</td>
<td>16.1 ± 9.0</td>
<td>15.9 ± 8.7</td>
<td>10.8 ± 9.7</td>
<td>11.3 ± 9.5</td>
<td>6.9 ± 8.2</td>
</tr>
<tr>
<td></td>
<td>DRS</td>
<td>97.0 ± 29.6</td>
<td>85.1 ± 36.4</td>
<td>80.2 ± 46.9</td>
<td>79.0 ± 41.7</td>
<td>79.0 ± 41.7</td>
<td>68.0 ± 53.1</td>
</tr>
<tr>
<td>Pure AD (n = 97)</td>
<td>MMSE</td>
<td>18.6 ± 8.4</td>
<td>14.6 ± 7.4</td>
<td>12.4 ± 8.4</td>
<td>10.6 ± 8.2</td>
<td>10.6 ± 8.2</td>
<td>7.5 ± 8.3</td>
</tr>
<tr>
<td></td>
<td>DRS</td>
<td>104.3 ± 21.1</td>
<td>90.4 ± 30.2</td>
<td>85.1 ± 30.6</td>
<td>75.6 ± 37.3</td>
<td>70.8 ± 38.5</td>
<td>59.0 ± 45.1</td>
</tr>
</tbody>
</table>

*MMSE indicates Mini-Mental State Examination; DRS, Dementia Rating Scale; and AD, Alzheimer disease.
†This group had AD and 1 or more small cerebral infarctions.

### Table 4. Annual Scores on the MMSE and the DRS in the Mixed and Pure AD Groups (Postadjustment, Matched on Age and Braak Stage)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Score, Mean ± SD</th>
<th>At Enrollment</th>
<th>1 y</th>
<th>2 y</th>
<th>3 y</th>
<th>4 y</th>
<th>5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n = 66)</td>
<td>(n = 48)</td>
<td>(n = 34)</td>
<td>(n = 32)</td>
<td>(n = 24)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>Mixed AD (n = 19)†</td>
<td>MMSE</td>
<td>17.3 ± 6.9</td>
<td>15.2 ± 9.0</td>
<td>15.2 ± 8.8</td>
<td>10.1 ± 9.8</td>
<td>10.2 ± 9.8</td>
<td>6.0 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>DRS</td>
<td>93.5 ± 28.8</td>
<td>81.3 ± 36.1</td>
<td>76.5 ± 47.4</td>
<td>72.0 ± 31.0</td>
<td>74.0 ± 47.4</td>
<td>59.0 ± 54.9</td>
</tr>
<tr>
<td>Pure AD (n = 47)</td>
<td>MMSE</td>
<td>17.5 ± 8.6</td>
<td>17.2 ± 8.0</td>
<td>15.6 ± 9.0</td>
<td>12.5 ± 9.1</td>
<td>11.7 ± 8.4</td>
<td>8.4 ± 9.0</td>
</tr>
<tr>
<td></td>
<td>DRS</td>
<td>101.6 ± 26.5</td>
<td>94.3 ± 31.5</td>
<td>92.8 ± 31.0</td>
<td>84.2 ± 36.5</td>
<td>86.4 ± 36.2</td>
<td>60.4 ± 45.1</td>
</tr>
</tbody>
</table>

*MMSE indicates Mini-Mental State Examination; DRS, Dementia Rating Scale; and AD, Alzheimer disease.
†This group had AD and 1 or more small cerebral infarctions.

### Table 5. Rate of Cognitive Decline Over Time in the Mixed and Pure AD Groups, Before and After Adjustment for Age and Braak Stage*

<table>
<thead>
<tr>
<th>Group</th>
<th>Score, Mean ± SD</th>
<th>Before Adjustment</th>
<th>After Adjustment</th>
<th>Slope Intercept P</th>
<th>Slope Intercept P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed AD†</td>
<td>MMSE</td>
<td>2.7 ± 0.3</td>
<td>18.5 ± 1.8</td>
<td>20</td>
<td>2.9 ± 0.1</td>
</tr>
<tr>
<td>Pure AD</td>
<td>3.2 ± 0.2</td>
<td>17.9 ± 0.8</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRS</td>
<td>11.7 ± 1.7</td>
<td>97.0 ± 7.6</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRS</td>
<td>13.2 ± 0.8</td>
<td>104.4 ± 3.3</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>

*AD indicates Alzheimer disease; MMSE, Mini-Mental State Examination; and DRS, Dementia Rating Scale.
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MMSE and 11.4 points on the DRS and suggested that the DRS, with its greater range, reflects the change with increasing dementia severity more precisely. The apparent disparity in the direction of change between the MMSE and the DRS score at the last examination (higher MMSE and lower DRS score in patients with mixed AD compared with those with pure AD) in the present study may reflect a more precise measurement by the DRS in the later stages of dementia. Also, since the DRS has a higher proportion of tests that measure “frontal” function (ie, attention and initiation/perseveration subscales) rather than memory and orientation relative to the MMSE, it is possible that the somewhat lower DRS scores may indicate a relative preponderance of “frontosubcortical” type deficits in our mixed group.

Random-effects models for longitudinal data analysis are suitable for recognizing the relation between serial observations on the same unit and dealing with highly unbalanced data, which is common with many longitudinal studies. Considerable variation among individuals in the number and timing of measurements, as in this study, caused unbalanced data sets that cannot be analyzed properly using a general multivariate model with an unrestricted covariance structure. In a random-effects model for longitudinal data, the probability distribution for the multiple measurements has the same form for each individual, but the distribution of these variables (random effects) varies among individuals. The slope (rate of annual decline), a random-effects variable calculated in this model, may differ from that obtained by simply calculating the cognitive score difference divided by the interval between testings (ie, \(\frac{[\text{initial MMSE (or DRS) score} - \text{last MMSE (or DRS) score}]}{\text{time}}\)) or by an ordinary least squares regression analysis, but the random-effects model for longitudinal data approach better represents the data provided in the present study.
This retrospective clinicopathologic study has some limitations. One, several selection biases were apparent (eg, patients with mixed AD generally had lower Braak stages and were older). Therefore, many subjects were excluded from some of the analyses to control for these confounding variables. Also, longitudinal neuropsychologic data attrition and the occasional unavailability of Braak stage decreased the number of patients analyzed. Furthermore, only the first 5 to 6 years of MMSE or DRS data were used in the rate of decline analyses. Also, we concentrated on only the mild concomitant infarcts with a volume of less than 10 cm³, resulting in a relatively small sample size, thereby lowering statistical power. At brain autopsy, the left hemisphere was examined in detail for AD and other pathological features, while the right hemisphere was only examined macroscopically. Examining only the left hemibrain histopathologically could result in missing some small unilateral infarcts in the right hemibrain.

Whether vascular pathological lesions have a threshold-lowering effect for the development of dementia when added to AD lesions or whether they somehow affect the initiation of AD remains unknown. The relative contribution to clinical dementia in patients with mixed AD with infarcts may well differ depending on the extent of the additional pathological lesions. The dosage effect of cerebral infarcts on dementia in patients with mixed AD needs to be examined further. The concept of vascular dementia being determined by the volume of infarcted tissue alone is probably oversimplistic. The effect of location and multiplicity of cerebral infarction needs to be examined further, as in one recent positron emission tomographic study. Given that there is considerable overlap between the volume, location, and number of infarcts across patients with and without dementia, it may be worthwhile to approach concomitant vascular pathological lesions in patients with AD from a perspective of their pathogenesis, ie, small- vs large-vessel disease. Microvascular, not macroscopic, disease was reported to be the chief substrate of vascular dementia in some neuropathologic series. It would be interesting to select patients with AD and infarcts presumably resulting from diffuse small-vessel disease of the brain and examine how such a vascular process might affect AD, relative to large-vessel disease or no cerebrovascular disease. This and other integrative approaches are needed before we can adequately understand the complex relation between cerebrovascular disease and AD.

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REFERENCES