Neuropathologic Basis of Age-Associated Brain Atrophy

Deniz Erten-Lyons, MD; Hiroko H. Dodge, PhD; Randall Woltjer, MD; Lisa C. Silbert, MD; Diane B. Howieson, PhD; Patricia Kramer, PhD; Jeffrey A. Kaye, MD

Importance: While brain volume changes are used as surrogate markers for Alzheimer disease neuropathology in clinical studies, the extent to which these changes are due to pathologic features of Alzheimer disease in the aging brain is not well established. This study aims to clarify the neuropathologic correlates of longitudinal brain atrophy.

Objective: To examine the association between brain atrophy during life and neuropathology in an elderly population.

Design: Autopsy study of a cohort of elderly individuals.

Setting: Community-based population.

Participants: Seventy-one healthy elderly individuals were selected from participants of the Oregon Brain Aging Study for having an autopsy, more than 1 magnetic resonance imaging scan, and the last magnetic resonance imaging scan within 36 months of death.

Main Outcomes and Measures: The associations between brain volume trajectories (ventricular, total brain, and hippocampal) and time interaction terms for neurofibrillary tangles, neuritic plaques, gross infarcts, microinfarcts, amyloid angiopathy, Lewy bodies, APOE ε4 presence, and clinical diagnosis (no cognitive impairment, mild cognitive impairment, or dementia as time-varying covariates) were examined in mixed-effects models, adjusting for duration of follow-up and age at death.

Results: Ventricular volume trajectory was significantly associated with age, presence of infarcts, neurofibrillary tangle and neuritic plaque scores, APOE ε4 allele presence, and dementia diagnosis. Total brain volume trajectory was significantly associated with age and mild cognitive impairment diagnosis. Hippocampal volume trajectory was significantly associated with amyloid angiopathy.

Conclusions and Relevance: Ventricular volume trajectory is more sensitive than total brain and hippocampal volume trajectories as a marker of accruing Alzheimer disease and vascular pathology in elderly individuals. The association between brain volume trajectories and cognitive impairment (mild cognitive impairment and dementia) remained after controlling for the degree of neuropathology and other covariates. This suggests that there may be other factors not measured in this study that could be contributing to brain atrophy in those with cognitive impairment.


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THERE IS AN INCREASING BODY of evidence showing that the clinical syndrome of Alzheimer disease (AD) in the elderly population may have a different pathologic correlate compared with younger individuals with AD.1-3 The contribution of mixed pathologies, especially AD and vascular pathology, to the clinical dementia syndrome in elderly individuals has been replicated in several autopsy series.4,6 These observations have led to timely editorials and reviews discussing (1) whether the clinical syndrome of AD across the age spectrum truly represents the same pathophysiological mechanisms and (2) whether there should be separate interventions aimed at treatment and prevention of AD in cases with young onset (ages <60 years), intermediate onset (ages 60-85 years), and late onset (ages >85 years).5,6

A related question is that of the neuropathologic correlates of longitudinal brain atrophy in elderly individuals. Brain volume changes are used as surrogate markers for AD neuropathology in clinical trials and biomarker studies. Yet, the extent to which these changes are due to pathologic features of AD in the aging brain is not well established. This study aims to clarify the neuropathologic correlates of longitudinal brain atrophy in an elderly community-based population.

To our knowledge, only 2 longitudinal studies correlated brain atrophy during life with neuropathologic measures obtained after death.10,11 These studies had discrepant findings. One of these studies found that ventricular and total brain vol-
ume changes were associated with both neuritic plaque (NP) and neurofibrillary tangle (NFT) burden in cognitively impaired individuals.\textsuperscript{11} The other study found a correlation only between NFTs and brain volume changes but not between a measure of total amyloid (that includes vascular and both diffuse plaques and NPs) and brain volume changes.\textsuperscript{10} We postulate that these discrepancies are a result of the age distribution of study participants in these studies (age ranges, 49-101 vs 68.9-106.2 years) as well as the differences in the timing of magnetic resonance imaging (MRI) scans (in relation to disease status and death). Our study specifically aims to understand the correlation between AD neuropathology and longitudinal brain atrophy in a homogeneous sample of elderly individuals who all had their first scan before onset of dementia. Our hypothesis is that, as has been observed with neuropathologic correlates of cognitive decline in elderly individuals,\textsuperscript{11} a mix of AD neuropathology and vascular disease will be associated with brain atrophy over time.

**METHODS**

**PARTICIPANTS**

Participants were healthy elderly individuals followed up as part of the Oregon Brain Aging Study.\textsuperscript{13} The Oregon Brain Aging Study began in 1989 at the National Institute on Aging’s Alzheimer’s Disease Center at Oregon Health and Science University.\textsuperscript{14} Community-dwelling elderly individuals aged at least 55 years who had no functional impairment, no comorbid illnesses, a baseline Mini-Mental State Examination score greater than 23,\textsuperscript{13} and a Clinical Dementia Rating (CDR) score of 0\textsuperscript{15} and exhibited no depression by screening with the Geriatric Depression Scale were included.\textsuperscript{17} In 2004, entry criteria were modified to include subjects with well-controlled, chronic medical conditions common with advanced age, such as hypertension and coronary artery disease, so that participants were more representative of the general population. Of the 376 subjects evaluated between March 3, 1989, and May 27, 2005, 305 met inclusion criteria and were enrolled. Of those 305 who were enrolled, 293 were aged at least 65 years. Attrition rates caused by loss to follow-up other than death were less than 1% per year. The institutional review boards of Oregon Health and Science University and the Portland Veterans Affairs Medical Center approved the studies. All volunteers signed written informed consent. Volunteers were examined every 6 months with the Mini-Mental State Examination,\textsuperscript{15} CDR,\textsuperscript{16} Cognistat,\textsuperscript{19} and neurological examination. Annually, a detailed battery of neuropsychological tests and brain MRI scans were performed.\textsuperscript{13,19} Performances on the Mini-Mental State Examination and Cognistat were included in the CDR rating. The apolipoprotein E gene (APOE) was genotyped using standard methods. Of the 193 Oregon Brain Aging Study participants who died during follow-up, 125 had an autopsy at death. Individuals with autopsy were older at entry to the study and at death but showed no differences in sociodemographic parameters, APOE ε4 allele distribution, duration of follow-up, and diagnoses compared with those who did not have an autopsy. In this study, participants were categorized into 3 cognitive groups based on their CDR score: no cognitive impairment (CDR score of 0), mild cognitive impairment (MCI) (CDR score of 0.5 and not meeting diagnostic criteria for dementia), and dementia (CDR score ≥0.5 and meeting diagnostic criteria for dementia). Diagnoses of possible or probable AD, vascular de-

**INCLUSION AND EXCLUSION CRITERIA**

Oregon Brain Aging Study volunteers were included if they met the following criteria: (1) had at least 2 MRI scans, with the last scan performed within 36 months of death; (2) had a cognitive evaluation done within 24 months of death; and (3) had a brain autopsy at death. Of the 125 subjects with autopsy, 74 met these criteria. Three outliers with brain volumes more than 3 SDs from the mean at any time were excluded. The remaining 71 volunteers were included in this study.

**MRI METHODS**

The MRIs were acquired with a 1.5-T magnet. The protocol consisted of continuous-slice, multiecho, multiplanar image acquisition with 4-mm-thick coronal slices and a 24-cm\textsuperscript{2} field of view using a 256 × 256 acquisition matrix with 2 excitations (repetition time, 2800 milliseconds; echo time, 30 and 80 milliseconds). To orient the coronal plane, T1-weighted sagittal images (repetition time, 600 milliseconds; echo time, 20 milliseconds) centered in the midsagittal plane were used.

A semiautomated image assessment program, REGION, was used for quantitative measurement of brain volumes.\textsuperscript{19,22} Image analysts were blinded to the volunteers’ clinical data and previous imaging results. Image analysis methods have been described previously.\textsuperscript{21} The intraclass correlation coefficient, assessing interrater reliability for volume measurements for all regions, was 0.9 or higher. Hippocampal, total brain, and ventricular volumes were measured as a proportion of intracranial volume.

**PATHOLOGIC METHODS**

Brains were examined for NFT and NP pathology and staged by the Braak and Consortium to Establish a Registry for Alzheimer’s Disease systems.\textsuperscript{23-25} Neuropathologic evaluation has been described previously.\textsuperscript{26}Brains were examined grossly as well as microscopically after being fixed in neutral-buffered formaldehyde solution for at least 2 weeks. For microscopic evaluation, tissue samples were taken from all cortical lobes bilaterally, frontal lobe white matter, anterior cingulate gyrus, hippocampus, amygdala, bilateral striatum and thalamus, midbrain, pons, medulla, and cerebellum. The NPs and NFTs were assessed unilaterally in most cases; cerebrovascular disease was assessed bilaterally. Six-micrometer sections from all these brain regions were stained with hematoxylin-eosin and Luxol fast blue for myelin. An occipital cortical section was stained with Congo red to evaluate the degree of amyloid angiopathy. A modified Bielschowsky silver impregnation method was used to identify diffuse plaques and NPs in the frontal and parietal cortex. Selected sections of the hippocampus and neocortical regions were immunostained with antibody to tau (tau2; Sigma). The presence of lacunar infarcts and large-vessel strokes was evaluated by both visual inspection and microscopic examination. Lesions were classified as microinfarcts if there was histologic evidence of tissue necrosis and gliosis that was not identified at gross examination of the brain. Subjects were coded to have gross infarcts if lacunes or large-vessel infarcts were present. The presence of Lewy bodies was determined histologically in the midbrain and nucleus locus ceruleus by evaluation of sections stained with hematoxylin-eosin and Luxol fast blue and by anti-a-synuclein immunohistochemistry performed on sections of amygdala and frontal cortex. Hippocampal sclerosis was
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 71)</th>
<th>Cognitive Impairmentb (n = 44)</th>
<th>No Cognitive Impairmentb (n = 27)</th>
<th>P Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, No. (%)</td>
<td>41 (57.75)</td>
<td>26 (59.09)</td>
<td>15 (55.6)</td>
<td>.77</td>
</tr>
<tr>
<td>Duration of follow-up, y</td>
<td>7.68 (3.59)</td>
<td>8.42 (3.38)</td>
<td>6.45 (3.63)</td>
<td>.02</td>
</tr>
<tr>
<td>Education, y</td>
<td>14.50 (2.91)</td>
<td>14.30 (3.15)</td>
<td>14.82 (2.49)</td>
<td>.48</td>
</tr>
<tr>
<td>Age at death, y</td>
<td>94.72 (5.46)</td>
<td>96.36 (5.05)</td>
<td>92.05 (5.11)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age at onset of cognitive impairment, y</td>
<td>NA</td>
<td>92.47 (5.29)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age at last cognitive evaluation, y</td>
<td>94.35 (5.49)</td>
<td>96.01 (5.06)</td>
<td>91.68 (5.17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time from last cognitive evaluation to death, mo</td>
<td>4.44 (3.24)</td>
<td>4.32 (3.48)</td>
<td>4.68 (2.88)</td>
<td>.63</td>
</tr>
<tr>
<td>Age at first MRI, y</td>
<td>88.36 (5.77)</td>
<td>89.21 (5.32)</td>
<td>86.98 (6.29)</td>
<td>.18</td>
</tr>
<tr>
<td>Age at last MRI, y</td>
<td>93.38 (5.27)</td>
<td>94.79 (4.95)</td>
<td>91.09 (5.05)</td>
<td>.003</td>
</tr>
<tr>
<td>Time from first MRI to death, y</td>
<td>6.85 (3.86)</td>
<td>7.77 (3.56)</td>
<td>5.34 (3.92)</td>
<td>.009</td>
</tr>
<tr>
<td>Time between first and last MRI, y</td>
<td>5.51 (3.61)</td>
<td>6.25 (3.46)</td>
<td>4.32 (3.59)</td>
<td>.03</td>
</tr>
<tr>
<td>Time from last MRI to death, mo</td>
<td>15.36 (9.96)</td>
<td>17.76 (9.96)</td>
<td>11.52 (8.88)</td>
<td>.009</td>
</tr>
<tr>
<td>≥1 APOE ε4 allele, No. (%)</td>
<td>15 (21.13)</td>
<td>8 (18.18)</td>
<td>7 (25.93)</td>
<td>.44</td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance image; NA, not applicable.

a Values are expressed as mean (SD) unless otherwise noted.
b Cognitive impairment indicates a Clinical Dementia Rating of 0.5 or higher; no cognitive impairment, a Clinical Dementia Rating of 0.
c t test for continuous variables and Pearson χ² test for categorical variables.

RESULTS

PARTICIPANT CHARACTERISTICS

The mean (SD) age at death was 94.72 (5.46) years (range, 80.1-108.1 years) (Table 1). Volunteers were followed up for a mean (SD) of 7.68 (3.59) years (range, 1.5-16.1 years). Of the 71 participants who enrolled while they were cognitively intact, 44 developed cognitive impairment. Of these, 20 had probable or possible AD, 5 had vascular dementia, 16 had MCI, and 3 had a mixed dementia as their last clinical diagnosis. The mean interval between the last MRI and neuropathologic evaluation was 15 months.

The group with no cognitive impairment had more individuals with lower Braak scores and fewer individuals with gross infarcts (Table 2).

MIXED-EFFECTS MODELS

More ventricular volume enlargement over time was significantly associated with older age (P < .001), diagnosis of dementia (P < .001), and presence of gross infarcts (P < .001), having gross infarcts (P < .001), and having moderate or frequent NPs (P < .001) (Figure 2), and presence of the ε4 allele (P < .001). There was a trend for association with MCI diagnosis (P = .04), age, and duration of follow-up (time from the first MRI to death) as potential confounders. Covariates were selected based on their previously established associations with longitudinal brain volume changes. We used JMP version 5.0.1a (SAS Institute, Inc), SAS version 9.2 (SAS Institute, Inc), and R version 2.11 (R Foundation) for statistical analyses. Significance was set at P < .017 (.05/3), the P value adjusted for 3 comparisons (ie, 3 volumetric measures) using the Bonferroni method.

COMMENT

In this clinicopathologic correlation study examining the neurodegenerative basis of brain atrophy, we observed that of the 3 volumes measured, ventricular volume trajectory compared with total brain and hippocampal volume trajectories had the strongest association with neuropathologic measures of AD and vascular disease.

There are several plausible explanations for ventricular volume trajectory showing a stronger association with...
pathologic measures. First, it may be due to the simple fact that ventricular volume measurements are more robust compared with other volumetric measurements. Because of the relatively smaller initial volume of the cerebrospinal fluid space, the percentage of increase in ventricular volume is proportionally more rapid than the percentage of loss of brain tissue.27 Thus, changes over time are easier and more robust to measure with less noise associated with repeated measurements. Alternatively, there may be a biological explanation: ventricular enlargement is a summary marker of atrophy in both gray matter (as a result of neuropil and neuronal loss) and white matter (as a result of axonal loss) associated with aging as well as changes in cerebrospinal fluid production and flow that occur during the aging process.27,28 It is possible that ventricular volume change correlates well with all these aging-related processes.

We also found that the presence of high NP scores was more significantly associated with ventricular volume enlargement compared with NFTs. This contradicts one previous study that found NFTs, but not a measure of total brain amyloid, to be associated with total brain atrophy and ventricular volume change.10 Several differences between this previous study and our study may have led to this discrepancy: the ages of the cohorts (median age at last scan was on average 10 years older and the age range of study participants was narrower in our study [80.1-108.1 vs 49-101 years, respectively]), timing of observations (in our study, participants were monitored for a longer period with ini-

### Table 2. Pathologic Parameters in Study Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (N = 71)</th>
<th>Cognitive Impairment (n = 44)</th>
<th>No Cognitive Impairment (n = 27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braak stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II, or no NFTs</td>
<td>27 (38.03)</td>
<td>11 (25.00)</td>
<td>16 (59.26)</td>
<td>.02a</td>
</tr>
<tr>
<td>III or IV</td>
<td>31 (43.66)</td>
<td>23 (52.27)</td>
<td>8 (29.63)</td>
<td></td>
</tr>
<tr>
<td>V or VI</td>
<td>13 (18.31)</td>
<td>10 (22.73)</td>
<td>3 (11.11)</td>
<td></td>
</tr>
<tr>
<td>CERAD NP burden</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or sparse</td>
<td>40 (56.34)</td>
<td>24 (54.55)</td>
<td>16 (59.26)</td>
<td>.69a</td>
</tr>
<tr>
<td>Moderate or frequent</td>
<td>31 (43.66)</td>
<td>20 (45.45)</td>
<td>11 (40.74)</td>
<td></td>
</tr>
<tr>
<td>Gross infarcts</td>
<td>24 (33.8)</td>
<td>19 (43.18)</td>
<td>5 (18.52)</td>
<td>.04b</td>
</tr>
<tr>
<td>Microinfarcts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>38 (53.52)</td>
<td>23 (52.27)</td>
<td>15 (55.56)</td>
<td>.52a</td>
</tr>
<tr>
<td>1</td>
<td>15 (21.13)</td>
<td>8 (18.18)</td>
<td>7 (25.93)</td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>18 (25.35)</td>
<td>13 (29.55)</td>
<td>5 (18.52)</td>
<td></td>
</tr>
<tr>
<td>Amyloid angiopathy</td>
<td>26 (36.62)</td>
<td>15 (34.09)</td>
<td>11 (40.74)</td>
<td>.62b</td>
</tr>
<tr>
<td>Hippocampal sclerosis</td>
<td>5 (7.04)</td>
<td>4 (9.09)</td>
<td>1 (3.70)</td>
<td>.64b</td>
</tr>
<tr>
<td>Lewy bodies</td>
<td>14 (19.72)</td>
<td>10 (22.73)</td>
<td>4 (14.81)</td>
<td>.54b</td>
</tr>
</tbody>
</table>

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; NFTs, neurofibrillary tangles; NP, neuritic plaque.

a Pearson χ² test.
b Fisher exact test.

Figure 1. Trajectories of ventricular volume change as a proportion of intracranial volume (ICV) for the Consortium to Establish a Registry for Alzheimer’s Disease neuritic plaque categories of none or sparse (A) and moderate or frequent (B). Dotted lines indicate the predicted trajectories based on estimates using the coefficients generated in the mixed-effects models; solid lines, the observed trajectories.
tial imaging obtained before onset of dementia), and assessment of amyloid pathology (NP score in our study vs a measure of total amyloid density in the other study). Two other studies found associations between measures of amyloid (NP scores in one study and carbon 11–labeled Pittsburgh Compound B positron emission tomography in the other) and ventricular volume enlargement rates, as we did.11,20

Another finding worth further discussion is that the presence of amyloid angiopathy was significantly associated with increased hippocampal volume loss and showed a trend for association with increased total brain volume loss. Two previous studies also found that the presence of amyloid angiopathy correlated with smaller cross-sectional hippocampal volumes.30,31 Some studies suggest that amyloid angiopathy is associated with reduced brain perfusion.32 Additionally, the hippocampus seems to be more vulnerable to brain hypoperfusion.33 It is possible that subtle, continuous, chronic ischemia from amyloid angiopathy may result in atrophy, more selectively observed in the hippocampus. This observation needs further investigation in future studies. It is not clear why the presence of amyloid angiopathy and not other AD neuropathologic markers correlated with hippocampal atrophy. One previous study also did not find an association of longitudinal hippocampal volume changes with NFTs and NPs.11 One possible explanation is that hippocampal volume changes due to AD neuropathology occur early in the course and plateau before changes in other volumes, whereas hippocampal volume loss continues in those with amyloid angiopathy. Results also may be influenced by the fact that hippocampal volume may be more prone to variability in longitudinal measurements. This may be related to more noise due to measurement techniques as well as possible biological fluctuations.34

Additionally, we found that ventricular volume enlargement accelerated during periods of dementia diagnosis and that total brain volume atrophy increased during periods of MCI diagnosis after adjusting for the presence of the neuropathologic measures. This suggests that brain volume changes in those with MCI or dementia cannot be solely explained by the amount of AD or vascular neuropathology. There likely are other factors not measured in this study that may be mediating the degree of brain atrophy in the presence of similar neuropathologic burden. For example, functional polymorphisms in genes in the apoptotic pathway or environmental influences on neurotrophins may mediate the degree of cell loss and in turn brain atrophy in the context of AD neuropathology.34,35 Alternatively, timing of the MRI observations in relation to cognitive evaluations may have contributed to this observation.

We also observed significant associations of the presence of gross infarcts and the APOE ε4 allele with ventricular volume trajectories. While it is not surprising to find that macroscopic infarcts are correlated with brain atrophy, it was surprising to find that the presence of the APOE ε4 allele was very strongly associated with the rate of change in ventricular volume. This finding was unexpected because it is thought that the effect of the APOE ε4 allele is most salient in young-old individuals compared with old-old individuals.36 A previous study from our center found a similar APOE ε4 effect on ventricular volume in women.37

This study has several limitations. Our sample size, although among the largest to assess the clinicopatho-
logic correlation of longitudinal brain volume trajectories, was nevertheless too small to examine the effects of less frequent pathologies, such as hippocampal sclerosis, or to categorize Lewy bodies as cortical vs noncortical. Additionally, assessments for other markers of pathogenic contributors to dementia, such as TAR DNA-binding protein 43, were not included. Our sample data are derived from volunteers in the 9th through 11th decades of life, a segment of the population at highest risk for cognitive impairment and death. Conclusions relative to younger at-risk individuals remain speculative at this point. The following are strengths of this study: (1) use of a well-described set of participants who were all enrolled as cognitively intact elderly individuals and followed up for a mean of 7.68 years until death, with multiple MRI scans and clinical assessments during life; (2) the inclusion of other confounding pathologic measures, such as vascular disease and Lewy bodies, in the analyses; and (3) use of mixed-effects models, which allowed for including participants with different durations of follow-up and for individual differences in time slope (random effects), and adjusting for the changing diagnoses over the duration of follow-up.

Our findings suggest that in individuals in the 9th through 11th decades of life, the trajectory of ventricular volume, but not other regional or total brain volumes, shows the strongest correlation with neuropathologic measures of AD and vascular disease. Given their relative ease of measurement, ventricular volume trajectories can be used when providing care or assessing potential new treatments for an increasingly elderly population. Additionally, our data suggest that the brain volume changes over time in those with cognitive impairment are different from those without cognitive impairment even after accounting for the degree of neuropathologic burden. This suggests that other mechanisms possibly related to cognitive reserve or resistance to atrophy may be modulating brain atrophy.

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Correspondence: Deniz Erten-Lyons, MD, Layton Aging and Alzheimer’s Disease Center, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, CR131, Portland, OR 97239 (erntenly@ohsu.edu).


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