Early-Onset Alzheimer's Disease Is Associated With Greater Pathologic Burden

Gad A. Marshall, MD, Lynn A. Fairbanks, PhD, Sibel Tekin, MD,
Harry V. Vinters, MD, and Jeffrey L. Cummings, MD

ABSTRACT

Two subtypes of Alzheimer's disease (AD) have been commonly identified: early- and late-onset forms. Previous studies suggest that early-onset AD patients have more neuritic plaques (NPs) and neurofibrillary tangles (NFTs). In the current study, NP and NFT counts were performed for 8 brain regions in 25 subjects with definite AD. A repeated-measures analysis of variance of mean regional NP and NFT counts for early- and late-onset groups was performed. A significant between-subject effect indicating greater overall NP and NFT burden in the early-onset group was observed (NP: $F = 6.8$, $df = 1$, $P = .015$; NFT: $F = 7.5$, $df = 1$, $P = .012$). This analysis supports the hypothesis that early-onset AD is associated with greater pathologic burden than late-onset AD. This suggests that late-onset AD patients have less cognitive reserve than early-onset patients and require fewer pathologic changes to exhibit cognitive deterioration. (*J Geriatr Psychiatry Neurol* 2007;20:29-33)

Keywords: Alzheimer's disease; early onset; late onset; pathology; neuritic plaques; neurofibrillary tangles

Two subtypes of Alzheimer's disease (AD) have been commonly identified: early-onset and late-onset AD, depending on whether disease onset occurs before or after the age of 65 years. Few studies have explored the differences in pathologic burden between these 2 groups of patients. The available data suggest that early-onset AD patients have greater synaptic loss and more neuritic plaques (NPs) and neurofibrillary tangles (NFTs) than late-onset patients.[1-5] The objective of this study was to examine the relationship between age at symptom onset and pathologic burden in AD. We postulated that early-onset AD subjects would have greater pathologic burden.

METHODS

Subjects

This was a retrospective cohort study. Twenty-five subjects with autopsy-verified definite AD (meeting the criteria of the Consortium to Establish a Registry for AD [CERAD][6]) were selected from the University of California, Los Angeles (UCLA), Alzheimer's Disease Research Center neuropathology database. All subjects met the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition) clinical criteria for dementia.[7] Subjects with other concomitant neurodegenerative diseases including dementia with Lewy bodies, Parkinson's disease, Huntington's disease, frontotemporal lobar degeneration, progressive supranuclear palsy, corticobasal degeneration, or multisystem atrophy were excluded. Subjects

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From the Department of Neurology (Drs Marshall, Vinters, and Cummings), Psychiatry and Biobehavioral Neuroscience (Drs Fairbanks and Cummings), and Pathology and Laboratory Medicine (Neuropathology; Dr Vinters), David Geffen School of Medicine, University of California, Los Angeles. From Florham Park, New Jersey (Dr Tekin).

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Address correspondence to: Gad A. Marshall, MD, Brigham and Women's Hospital Department of Neurology, Memory Disorders Unit, M97, 221 Longwood Ave., Boston, MA 02115; e-mail: gamarchall@partners.org.

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Table 1. Demographics of Subjects

	Early Onset	*Late Onset*	t *or* χ^2 *Value*	P *Value*
Gender, % female	55	79	1.6	0.20
Age at symptom onset, y	57.5 ± 6.0	74.6 ± 6.5	—	—
Range	43-63	65-89	—	—
Age at death, y	68.9 ± 6.4	83.4 ± 7.1	5.3	.00002
Range	59-78	73-99		
Dementia duration, y	11.4 ± 5.6	8.9 ± 3.3	1.4	.18
Education, y	14.1 ± 2.0	14.4 ± 2.5	0.3	.78
Family history, % positive	18	7	0.7	.70
Last MMSE	6.4 ± 4.7	6.5 ± 6.7	0.04	.97

Note: Early-onset Alzheimer's disease (n = 11) and late-onset Alzheimer's disease (n = 14), except for family history (early onset n = 9, late onset n = 11) and Mini-Mental State Examination (MMSE) data (early onset n = 10, late onset n = 12). Values represent means with standard deviations (except for gender and family history).

with extensive cerebrovascular disease including cortical infarcts, multiple lacunar infarcts, or cerebral hemorrhages and subjects meeting criteria for vascular dementia were excluded as well.

Genetic analysis for familial AD mutations (presenilin 1, presenilin 2, and amyloid precursor protein) was not performed, but family history of first-degree relatives with AD was reported. Age at symptom onset in first-degree relatives was not available. Nearly all subjects with a known cause of death died of pneumonia, although this was not always confirmed at autopsy because for many subjects, only the brain was examined. This is in agreement with a prior large autopsy series, which reported bronchopneumonia as the most common cause of death in dementia.[8]

Subjects with age at symptom onset less than 65 years were defined as early onset (n = 11), and subjects with age at symptom onset equal to or greater than 65 years were defined as late onset (n = 14). See Table 1 for the demographics of subjects. The mean interval from Mini-Mental State Examination (MMSE) administration to autopsy was 23.7 ± 22.0 months; there was no significant difference in MMSE interval between the 2 age groups (t = 1.7, P = .13).

The study was approved by the UCLA Institutional Review Board. Subjects provided consent for a research autopsy during initial clinical research evaluations prior to knowing the course of their disease. Once subjects expired, informed consent was obtained from subjects' caregivers after the current study's procedures were fully explained.

Neuropathologic Data

The mean postmortem interval was 22.8 ± 14.4 hours. NP and NFT counts were performed on all brain autopsy specimens by 2 investigators blinded to age group status. Interrater and intrarater reliability (mean rater intraclass correlation coefficients) for counts were 0.95 to 0.98 and 0.96 to 0.97, respectively. Eight brain regions commonly sampled in the CERAD protocol[6] were evaluated: right and left orbital frontal cortex (Brodmann area [BA] 11), anterior cingulate cortex (BA 24), lateral parietal cortex (BA 7), superior temporal cortex (BA 21/22), occipital cortex (BA 19), CA1 region of the hippocampus, and prosubiculum.

Lesion counts were performed on Bielschowsky-stained sections at a magnification of 200 × using a 1-mm^2 graticule (grid), as previously reported.[9] Five randomly selected linear fields, spanning the whole cortical thickness, were counted for each brain region. The mean of the 5 fields was calculated, and counts were reported as lesion density per millimeter squared of tissue. For hippocampal areas, only 2 fields were selected because of the small size of the CA1 sector and the prosubiculum.

Braak staging (I-VI) was performed, as previously reported by Braak and Braak.[10] To evaluate for the presence of cortical Lewy bodies, α-synuclein immunostained sections were examined in all subjects. None of the subjects had cortical Lewy bodies. Diffuse cerebral atrophy was reported qualitatively as follows: 0 = absent, 0.5 = minimal, 1 = mild, 2 = moderate, and 3 = severe.

Data Analysis

Missing Values Replacement

For each brain region, data were available for 20 or more (of 25) subjects. Because of limited tissue availability for Bielschowsky staining, not all subjects had the 8 brain regions used in our protocol. Up to 3 missing values of specific regions were replaced per subject with the mean value for each region (the mean was derived from all subjects). The total number of missing values replaced was 21 of 200 values, or 10.5% (12 of 88 [14%] for early-onset subjects and 9 of 112 [8%] for late-onset subjects; χ^2 = 1.6, P = .29).

Demographic variables, including last MMSE prior to death, dementia duration, education, gender, and family history, were screened for differences between early- and late-onset subjects using t tests for continuous variables and a χ^2 test of independence for gender and family history. Diffuse cerebral atrophy was similarly screened.

Differences between early- and late-onset groups in NP and NFT counts were tested using a repeated-measures

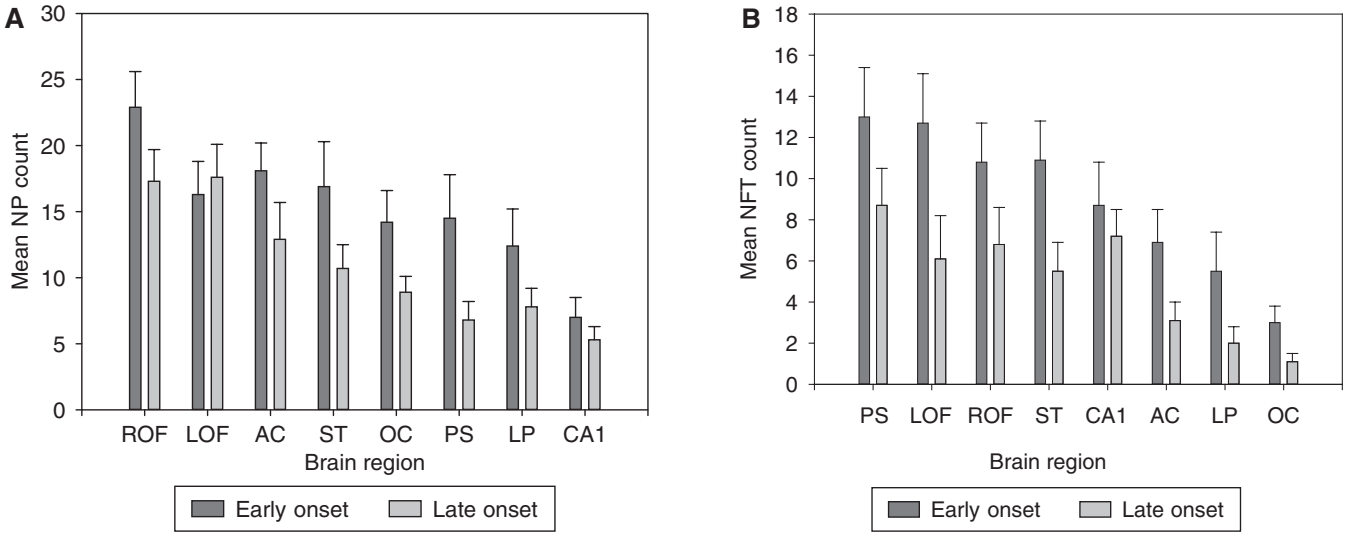

Figure 1. Mean regional neuritic plaque (NP) and neurofibrillary tangle (NFT) counts for early- and late-onset Alzheimer's disease (AD). (A) For NP counts, a significant between-subject effect ($F = 6.8$, $df = 1$, $P = .015$) is seen without a significant interaction between region and age group ($F = 1.0$, ns). (B) For NFT counts, a significant between-subject effect ($F = 7.5$, $df = 1$, $P = .012$) is seen without a significant interaction between region and age group ($F = 0.7$, ns). Brain regions are listed left to right in order of greatest regional NP and NFT density. NP and NFT counts are reported in per mm^2. Error bars represent standard error of the mean. ROF, right orbital frontal; LOF, left orbital frontal; AC, anterior cingulate; ST, superior temporal; OC, occipital; PS, prosubiculum; LP, lateral parietal; CA1, CA1 region of the hippocampus.

analysis of variance (ANOVA), with age of onset as a between-subjects factor and brain region as a within-subject variable. The Greenhouse-Geisser correction was used for the within-subject analyses. Main effects and interactions of region and age of onset are reported as F and P values. Dementia duration and gender were added as covariates to determine their effect on the outcome. This was done because of the large absolute differences in these values between the early- and late-onset groups despite the lack of statistical significance, which could have been due to the small sample size (see Table 1). An additional subanalysis excluding the 2 early-onset subjects with a positive family history was performed.

RESULTS

Mean age at symptom onset was 57.5 ± 6.0 years (range, 43-63) for the early-onset group and 74.6 ± 6.5 years (range, 65-89) for the late-onset group. Demographic characteristics of the 2 groups are shown in Table 1. Mean NP count was 15.6 ± 4.5/mm^2 for the early-onset group and 11.0 ± 5.1/mm^2 for the late-onset group. Mean NFT count was 9.3 ± 4.3/mm^2 for the early-onset group and 5.1 ± 3.6/mm^2 for the late-onset group. Mean Braak stage was V to VI (5.6 ± 1.0 for the early-onset group and 5.4 ± 0.7 for the late-onset group). There was no significant difference in diffuse cerebral atrophy between the early-onset and late-onset groups, both of which exhibited a mild to moderate degree of atrophy (1.7 ± 1.1 for the early-onset group and 1.4 ± 0.7 for the late-onset group; $t = 0.6$, $P = .56$).

There was a significant difference in mean age at death between the early- and late-onset groups ($t = 5.3$, $P < .0001$). There were no significant differences in other demographic features. Mean NP count correlated significantly with mean NFT count ($r = 0.56$, $P = .004$). Braak stage correlated significantly with mean NP and NFT counts (NP: $r = 0.45$, $P = .035$; NFT: $r = 0.65$, $P = .001$).

Figure 1A shows the mean NP counts by region and by age-of-onset group. The repeated-measures ANOVA for NP counts revealed significant differences across brain regions (region: $F = 9.3$, $df = 4.7$, $P < .0001$) and significantly greater counts for early-onset versus late-onset subjects (age of onset: $F = 6.8$, $df = 1$, $P = .015$). There was no significant interaction between region and age group ($F = 1.0$, ns), indicating that the greater NP burden for the early-onset group was relatively consistent across brain regions. Similar results were found for NFT counts, shown in Figure 1B. There were significant differences in NFT counts across brain regions (region: $F = 9.5$, $df = 3.7$, $P < .0001$) and significantly greater counts for early-onset versus late-onset subjects (age of onset: $F = 7.5$, $df = 1$, $P = .012$). There was no significant interaction between region and age group ($F = 0.7$, ns), suggesting that the effect of age of onset on NFT burden was not restricted to specific regions.

Inclusion of dementia duration or gender as covariates in the ANOVA models did not alter the significance of the results for either measure (age of onset, NP: $F = 7.3$, $df = 1$, $P = .013$; NFT: $F = 10.5$, $df = 1$, $P = .004$).

The results of the subanalysis excluding the 2 early-onset subjects with a positive family history were similar to the above results (age of onset, NP: $F = 6.8$, $df = 1$, $P = .017$; NFT: $F = 6.9$, $df = 1$, $P = .016$; including dementia duration or gender as covariates, NP: $F = 6.4$, $df = 1$, $P = 0.021$; NFT: $F = 11.2$, $df = 1$, $P = .003$).

DISCUSSION

This comparison of early- and late-onset AD corroborates prior studies showing that late-onset subjects with age at symptom onset greater than 65 years have less pathologic burden.[2,4] This finding was not influenced by dementia severity (represented by MMSE score) or duration, which were not significantly different for the 2 groups. Our results suggest that late-onset AD patients have less cognitive reserve[11] than early-onset patients do, requiring less pathologic burden to manifest cognitive changes. As people age, the threshold required to yield cognitive deficits is lowered.

In this analysis, no specific region drove the difference in pathologic burden between the early- and late-onset groups. Prior studies have demonstrated associations with frontal and parietal pathologic burden.[2,4] The sample size of the current study was not large enough to detect an interaction between age of onset and brain region that would support the hypothesis that some regions are affected more than others. With a larger sample size, this question can be better addressed.

Certain factors, such as premorbid intellectual function and education, have been suggested to be protective against AD, suggesting that people with more education have greater brain reserve.[12] In the current study, after controlling for dementia severity (represented by MMSE score), there was a significant positive correlation between education and pathologic burden (NP: partial $r = 0.54$, $P = .016$), as previously demonstrated in functional imaging studies,[13] further strengthening the cognitive reserve hypothesis.

Braak staging[10] correlated significantly with mean NP and NFT counts, more so with the latter, further validating the counts performed in this study. The CERAD[6] and National Institute on Aging and Reagan Institute[14] criteria for the diagnosis of AD require greater NP burden to make a diagnosis in older patients. Therefore, the results of the current study and prior similar studies demonstrating lower pathologic burden in older AD patients suggest that the current pathologic criteria for AD may be underdiagnosing older patients.

The limitations and weaknesses of this study were as follows. First, the counting method consisted of a 2-dimensional (2-D) nonstereological approach. The NP and NFT regional density values reported in this study cannot be accurately converted to regional volume values as those reported in neuron-counting studies using 3-D design-based stereological methods. 2-D counting makes various biased assumptions about lesion shape, orientation, size, and distribution.[15] Moreover, 2-D nonstereological counting does not correct for tissue shrinkage or expansion that occurs during tissue preparation and fixation and the age-dependent differential shrinkage that has been observed.[16] However, we did not find a significant difference in diffuse cerebral atrophy between early-onset and late-onset subjects. Nonetheless, the absolute values for NP and NFT counts and individual regional analyses reported here should be interpreted with caution. Second, apolipoprotein E genotyping and familial AD genetic analyses were not performed, but family history was reported: there was no significant difference between the early- and late-onset groups in this small sample. Since only 18% of early-onset AD subjects had a positive family history, it is likely that nearly all subjects in the current study had sporadic rather than familial AD. Moreover, the subanalysis excluding the early-onset subjects with a positive family history yielded similar results to the primary analysis. Third, these results need to be replicated with a larger sample before further conclusions can be drawn, especially for regional effects.

In summary, late-onset AD subjects had less pathologic burden than early-onset subjects did, suggesting that late-onset AD patients have less cognitive reserve.

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