Role of the Neuropathology of Alzheimer Disease in Dementia in the Oldest-Old

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Background: Neuritic plaques (NPs) and neurofibrillary tangles (NFTs) in the brain, especially in the hippocampus, entorhinal cortex, and isocortex, are hallmark lesions of Alzheimer disease and dementia in the elderly. However, this association has not been extensively studied in the rapidly growing population of the very old.

Objective: To assess the relationship between estimates of cognitive function and NP and NFT pathologic conditions in 317 autopsied persons aged 60 to 107 years.

Design: We studied the relationship between severity of dementia and the density of these characteristic lesions of Alzheimer disease in young-old, middle-old, and oldest-old persons. The relationship of the severity of dementia as measured by the Clinical Dementia Rating scale to the density of NPs and NFTs was then assessed in each age group.

Participants: Three hundred seventeen brains of persons aged 60 years and older were selected to have either no remarkable neuropathological lesions or only NP and NFT lesions. Brains with any other neuropathological conditions, either alone or in addition to Alzheimer disease findings, were excluded. The study cohort was then stratified into the youngest quartile (aged 60-80 years), middle 2 quartiles (aged 81-89 years), and oldest quartile (aged 90-107 years).

Results: While the density of NPs and NFTs rose significantly by more than 10-fold as a function of the severity of dementia in the youngest-old group, significant increases in the densities of NPs and NFTs were absent in the brains of the oldest-old. This lack of difference in the densities of NPs and NFTs was due to reduced lesion densities in the brains of oldest-old persons with dementia rather than to increased density of these lesions in the brains of nondemented oldest-old persons.

Conclusions: These findings suggest that the neuropathological features of dementia in the oldest-old are not the same as those of cognitively impaired younger-old persons and compel a vigorous search for neuropathological indices of dementia in this most rapidly growing segment of the elderly population.

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Nervous plaques (NPs) and neurofibrillary tangles (NFTs), mainly in the neocortex, the entorhinal cortex, and the hippocampus, represent the hallmark neuropathological lesions of Alzheimer disease (AD). Most studies have found the densities of NPs and NFTs to be associated with the severity of cognitive deficits, although the relative contributions of NPs and NFTs to cognitive dysfunction continue to be debated. The different neuropathological diagnostic systems in common use, such as the Khachaturian criteria, the Consortium to Establish a Registry for Alzheimer Disease (CERAD) criteria, and the National Institute on Aging–Reagan Institute criteria, use the density of these lesions and their association with dementia to arrive at a diagnosis of AD with varying degrees of certainty.

The pivotal studies that have laid the foundation for our understanding of the relationship between lesion density and cognitive impairment have been conducted most frequently in individuals dying in the seventh through ninth decades of life. However, US Census Bureau data project that the number of Americans older than 85 years will increase more rapidly than any other group, quadrupling from 4.4 million in 2001 to 19.3 million by 2050. Of these 19.3 million, more than 8 million are predicted to suffer from dementia, whereby in addition to personal and caregiver suffering, the inflation-
unadjusted cost of care in this population will rise to more than $33 billion. Furthermore, a recent study has shown that even after controlling for physical disorders, 5-year mortality rate in persons aged 95 years and older is significantly higher in demented individuals than in cognitively intact persons (96.0% vs 73.0%, respectively). Dementia was a stronger predictor of mortality in this population than cardiovascular disease, cancer, or being male. These observations underscore the necessity for understanding the relationship between cognitive impairment and the neuropathologies of dementia in the oldest-old.

The number of studies of the neuropathological correlates of cognitive dysfunction in persons who are aged 85 years and older are few, and they often focus on cases that meet clinical or neuropathological criteria for AD. However, the validity of the neuropathological criteria for diagnosing AD in this age group can be questioned. The CERAD criteria, for example, treat all persons older than 75 years uniformly, suggesting an underlying assumption of uniformity of the interaction of clinical and pathological indices in persons older than 75. Studies of the relationships between direct measures of cognitive function and estimates of lesion density are rarer. In general, qualitative and quantitative studies have found the neuropathological correlates of cognitive impairment in AD to be more variable and often less profound in persons older than 85 or 90 years than in younger persons, but note that Nelson et al present opposing results.

Given the potential ambiguity of relying on clinical or neuropathological diagnoses of AD in the oldest-old, the current study assessed the relationship between estimates of cognitive function and NP and NFT pathologic conditions in 317 autopsied persons aged 60 to 107 years. These cases included persons who had either no significant neuropathological features or only NP and NFT neuropathological features. Persons with non-AD clinical conditions known to lead to cognitive impairment (eg, schizophrenia, major depression) and persons with non-AD neuropathologies as defined by CERAD (eg, significant cerebrovascular lesions, Lewy bodies with or without NPs and NFTs) were excluded. The 317-member study cohort was then stratified by age at death into quartiles, and the association of NPs and NFTs with cognitive impairment was assessed in the youngest (youngest-old), middle 2 (middle-old), and oldest (oldest-old) age quartiles.

**METHODS**

**SUBJECTS**

All antemortem and postmortem procedures were approved by the Mount Sinai School of Medicine and Jewish Home and Hospital institutional review boards. Postmortem brains, donated by the next of kin of deceased residents of the Jewish Home Hospital and other facilities participating in studies of aging and early dementia, were received over a period of 25 years by the Mount Sinai School of Medicine Department of Psychiatry Brain Bank. Analyses were based on the brains of 317 consecutively autopsied donors who met the inclusion criteria described later.

Research staff blind both to the hypotheses tested and neuropathological findings performed neuropsychological tests, reviewed detailed medical records, and, whenever possible, conducted in-depth interviews with caregivers to obtain information about antemortem medical, neurological, psychiatric, functional, and cognitive status. Donors were included in the study if they met CERAD neuropathological criteria for normal brain, definite AD, probable AD, or possible AD only, as described previously.

**DEMENTIA STAGING**

The Clinical Dementia Rating (CDR) scale assesses cognitive and functional impairments associated with dementia and classifies subjects as nondemented (CDR score of 0), questionably demented (CDR score of 0.5), or without increasing levels of severity of dementia (CDR score of 1 to 5). A previously described multistep approach that included independent ratings by research psychometricians (V.H., M.S.-B., D. Purohit, D. Perl, G.T.L., M.M., H.T.G.) and a consensus conference that included evaluation of all available neuropsychological test results and caregiver interviews was applied to the assignment of CDR on the basis of stable (nonagonal) cognitive and functional status during the last 6 months of life.

**NEUROPATHOLOGICAL ASSESSMENT**

The neuropathological assessment procedures used have been described extensively and followed CERAD consensus recommendations. Standardized representative blocks from the neocortex (superior and midfrontal gyrus, orbital cortex, superior temporal gyrus, inferior parietal lobule of the parietal cortex, and caudate nucleus), basal ganglia with basal forebrain, amygdala, hippocampus (rostral and caudal levels with adjacent entorhinal, parahippocampal, and temporal cortex), rostral cingulated gyrus, corpus striatum, thalamus, midbrain, pons, medulla, cerebellar vermis, and lateral cerebellar hemisphere were examined using hematoxylin-eosin, modified Bielschowsky, and modified thioflavin S stains. Persons with Lewy body formation in the substantia nigra or locus ceruleus underwent anti-ubiquitin or α-synuclein staining of representative cerebral cortical sections. Neuropathological assessments were conducted blindly (D. Purohit and D. Perl) to all clinical and psychometric data. Every person was evaluated for the extent of neuropathological lesions using the CERAD neuropathological battery for the extent of NPs and NFTs using a 4-point scale (0 indicates none; 1, sparse; 3, moderate; and 5, frequent). In addition, quantitative data regarding the density of NPs that were collected in 5 cortical regions using previously published methods were expressed as mean plaque density per square millimeter for that region: the midfrontal gyrus (Brodmann area 9), orbital frontal cortex (Brodmann area 45/47), superior temporal gyrus (Brodmann area 21/22), inferior parietal lobule (Brodmann area 39), and calcarine cortex (Brodmann area 17). The primary rating variables used in the analyses reported here were densities of NPs and NFTs in the entorhinal cortex, hippocampus, amygdala, and the neocortical regions. Density estimates of NPs and NFTs from the subcortical fields did not substantively contribute to the results described and were not included in analyses.

**STRATIFICATION OF THE STUDY COHORT INTO AGE GROUPS**

Quartile age ranges were calculated for the entire study cohort (60-107 years of age). Subjects were assigned to 3 groups consisting of the youngest age quartile (young-old; mean age, 71.4...


Table 1. Demographic Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th>CDR Score</th>
<th>No. of Subjects</th>
<th>Mean (SD) Male/Female Age, y</th>
<th>Mean (SD) PMI WBHO</th>
<th>No. of Subjects by Race</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>W</td>
</tr>
<tr>
<td>0</td>
<td>35</td>
<td>69.4 (0.96) 18/17</td>
<td>19.0 (2.5)</td>
<td>25</td>
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<tr>
<td>0.5</td>
<td>9</td>
<td>70.3 (2.15) 5/4</td>
<td>8.1 (2.6)</td>
<td>8</td>
</tr>
<tr>
<td>1.0</td>
<td>7</td>
<td>74.3 (1.64) 2/5</td>
<td>8.8 (2.9)</td>
<td>4</td>
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<tr>
<td>2.0</td>
<td>6</td>
<td>76.3 (1.69) 4/2</td>
<td>18.9 (9.1)</td>
<td>3</td>
</tr>
<tr>
<td>3.0</td>
<td>17</td>
<td>76.1 (1.07) 7/10</td>
<td>11.3 (2.7)</td>
<td>13</td>
</tr>
<tr>
<td>4.0</td>
<td>6</td>
<td>67.3 (1.26) 4/2</td>
<td>16.7 (5.8)</td>
<td>3</td>
</tr>
<tr>
<td>5.0</td>
<td>15</td>
<td>69.1 (1.48) 12/3</td>
<td>7.8 (1.8)</td>
<td>13</td>
</tr>
</tbody>
</table>

Middle Group (Age Range, 81-89 y)

|           |                 |                               |                     | W | B | H | O |
| 0         | 11              | 84.7 (0.85) 1/10              | 8.4 (1.7)           | 11 | 0 | 0 | 0 |
| 0.5       | 9               | 85.7 (0.78) 3/6               | 12.8 (5.4)          | 8  | 1 | 0 | 0 |
| 1.0       | 12              | 84.7 (0.84) 6/6               | 8.5 (2.5)           | 10 | 2 | 0 | 0 |
| 2.0       | 12              | 83.9 (0.51) 3/9               | 12.1 (3.8)          | 9  | 1 | 1 | 1 |
| 3.0       | 23              | 85.1 (0.48) 4/19              | 9.8 (2.7)           | 19 | 4 | 0 | 0 |
| 4.0       | 18              | 84.0 (0.92) 8/10              | 11.2 (3.8)          | 15 | 2 | 1 | 0 |
| 5.0       | 21              | 96.0 (0.48) 4/17              | 3.9 (0.5)           | 19 | 1 | 1 | 0 |

Oldest Group (Age Range, 90-107 y)

|           |                 |                               |                     | W | B | H | O |
| 0         | 7               | 96.4 (1.56) 2/5               | 8.3 (2.3)           | 7  | 0 | 0 | 0 |
| 0.5       | 8               | 92.7 (0.59) 4/4               | 7.7 (2.6)           | 5  | 1 | 1 | 1 |
| 1.0       | 10              | 95.8 (1.49) 1/9               | 11.6 (5.0)          | 10 | 0 | 0 | 0 |
| 2.0       | 16              | 94.1 (1.07) 3/13              | 10.8 (2.9)          | 15 | 0 | 0 | 1 |
| 3.0       | 36              | 93.4 (0.60) 6/30              | 7.2 (1.3)           | 29 | 5 | 2 | 0 |
| 4.0       | 21              | 94.1 (0.67) 4/17              | 12.5 (4.9)          | 19 | 2 | 0 | 0 |
| 5.0       | 18              | 96.0 (0.78) 2/16              | 5.7 (1.0)           | 16 | 1 | 1 | 0 |
| All ages and CDRs | 317   | 84.4 (0.58) 103/214       | 10.5 (0.7)          | 261 | 34 | 16 | 6 |

Abbreviations: B, Black; CDR, clinical dementia rating; H, Hispanic; O, other; PMI, postmortem interval (in hours); W, White.

Statistical Analyses

The densities of NPs and NFTs in the different brain regions and the summary variables described earlier were analyzed by factorial analyses of variance using Statistica (version 6.1; StatSoft Inc, Tulsa, Oklahoma). Separate analyses of variance tests were run to test the associations of age quartile and CDR at death with NP and NFT density in each of the predefined brain regions described earlier. Tukey's honestly significant difference tests were used for post hoc analyses. In each post hoc analysis, the density of NPs or NFTs in subjects with a CDR score of 0 in each age group was compared with subjects with CDR scores of 0.5, 1, 2, 3, 4, or 5.

Results

The 3 age groups did not differ from each other with respect to distribution of APOE4 genotype (χ²< 1.62, P = .10). The principal results of this study are summarized in Figure 1 and Table 2. This figure shows the fold change in the aggregate density of NFTs (top panel) and NPs (bottom panel) in persons with severe cognitive deficits (CDR = 5) relative to cognitively intact persons in the 3 age groups. The results of analyses based on the specific regions of the brain examined were similar to those shown for all of the examined regions in aggregate. Analyses of variance for mean NP density revealed significant effects of age groups (F2,296 = 6.9; P = .002), CDR groups (F0,296 = 19.9; P < .001), and age group by CDR interaction (F1,296 = 1.76; P = .046). The density of NPs was significantly increased (P < .02) in subjects with CDR scores of 2, 3, 4, and 5 in the youngest-old age group and in subjects with CDR scores of 5 in the middle-old age group, but no CDR-associated significant differences in NP density were detected in the oldest-old group (P > .7). A similar pattern of significant associations and interactions was noted for the density of NFTs in these same groups: age groups (F2,297 = 4.1; P = .02), CDR (F0,296 = 27.6; P < .001), and age-by-group interaction (F1,296 = 2.8; P = .002). Post hoc analyses revealed that while subjects in the young-old and middle-old age groups with CDR scores of 2, 3, 4, and 5 evidenced significantly greater (P < .02) densities of NFTs, the density of NFTs in none of the cognitively impaired groups in the oldest-old age group differed significantly (P > .68) from the cognitively unimpaired (CDR = 0) subjects. Similar patterns of NP and NFT density as a function of age grouping and CDR were revealed when the densities of NPs and NFTs were examined in individual brain regions (individual statistical analyses not shown). As expected, the occipital cortex showed less NP and NFT involvement. Significant differences from

years; range, 60–80 years), the middle 2 age quartiles (middle-old; mean age, 84.9 years; range, 81–89 years), and the oldest age quartile (oldest-old; mean age, 94.4 years; range, 90–107 years) (Table 1). Quartiles were defined by first calculating the median of the ordered age range of the study cohort and then dividing each half by the median of that half. The 3 groups differed in their composition by sex. As expected from population trends, the proportion of women in the 2 older age groups was significantly greater (χ² > 6.2; P < .02 for all) than in the youngest age quartile.

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The results of this study show that the nearly universally replicated rise in NP and NFT densities that is observed in persons who are 60 to 80 years of age and transition from normal cognition to dementia is absent in similarly demented nonagenarians and centenarians. This observation is consistent with previous findings that have pointed to the greater incidence of dementia in the oldest-old in the absence of clear neuropathological sequelae or divergence of regions of vulnerability and changes in the neuropathological phenotype of cognitively impaired nonagenarians and centenarians. Other studies have noted the presence of hallmark AD lesions in the brains of very old persons with no obvious dementia. In contrast, a recent study has suggested that the relationship between NFTs and cognitive impairment may be more profound in persons older than 90 years than in younger cohorts. Given the overall similarity of the procedures used in that study and those described here and by others, the reasons for the differences in results are unclear. One consequence of this changing or inconsistent neuropathological phenotype is to raise questions concerning the age-associated algorithms, formal or informal, that we apply to the diagnosis of AD. As mentioned previously, most neuropathological criteria for the diagnosis of AD incorporate an underlying assumption of an age-associated and dementia-independent rise in NP and NFT features. Therefore, the “burden of proof” for a diagnosis of AD rises with age.
such that greater and greater densities of NPs and/or NFTs are required for the diagnosis. This study raises the possibility of a need to reconsider or refine the application of a monotonic age-associated scale to the way that we think about the neuropathological features of AD and weigh the utility of considering the influence of age on NP and NFT density as an inverted U-shaped or non-monotonic function.

Alternatively, it may be heuristically advantageous to think of the association of different underlying neurobiological mechanisms with cognitive impairment and dementia in relatively young elderly persons vs the oldest-old. The generally weak association of NPs and NFTs with dementia in the oldest-old have led some to challenge the importance of these lesions to dementia in the oldest-old and others to suggest that microvascular pathological correlates may be an important determinant of cognitive dysfunction in the oldest-old. Abnormalities of synaptic structure and function represent another one of many possible neurobiological functions that may be better correlates of dementia in the oldest-old. Recent studies have extended the now classic and often replicated observations of the strong association of indices of synaptic loss or dysfunction with cognitive impairment in AD to the oldest-old.

It may be argued that dementia in the oldest-old is associated with other known pathological correlates of dementia such as large-vessel cerebrovascular disease and Lewy body disease. Although these and other neuropathological correlates of dementia may well be associated with dementia in the oldest-old in the general population, such an association is an unlikely explanation for the current study. In this study we specifically excluded from the analyses the brains of donors that had lesions other than NPs and NFTs; however, the overall conclusions of the study were not changed when 110 persons with comorbid cerebrovascular disease (CERAD diagnostic criteria), 86 of whom (78.0%) were in the oldest-old age quartile, were included in the study cohort and the data reanalyzed (data not shown). Another factor of potential significance is the level of education of the participating subjects and their cognitive reserve. Data on years of education were available on a relatively small subset of the study subjects owing to lack of detailed knowledge of distant histories by informants and lost historical educational records. However, there were no differences between the 3 age groups with respect to the proportion of subjects on whom data on years of education were available, nor were there any differences between the 3 age groups in their levels of education (mean, 13.2 years). Although the incompleteness of the available data on level of education in the study cohort demands a high level of caution, the similarity of the groups with respect to education suggests that level of education and perhaps cognitive reserve are unlikely strong determinants of the lack of association of NP and NFT densities with cognitive deficits in the oldest-old group studied here.

United States and world population trends show that by 2050 the population of persons living over the age of 85 years is estimated to rise to 19.3 million, and some
40.0% to 50.0% of these elderly will experience dementia. The results of the current study suggest that the neuropathological correlates of dementia in the oldest-old are likely to be different than the NP and NFT lesions that we have come to associate most directly with dementia in the youngest-old or in the middle-old. This observation may have significant consequences for how we think about dementia in the oldest-old, how we consider the criteria for AD diagnosis, how we research the neurobiological substrates of dementia in the aged, and the therapeutic avenues that we use to treat dementia in the rapidly growing oldest-old subgroup of the elderly. One speculative yet intriguing possibility for studies of the neurobiological substrates of dementia suggested by these results is that the study of the neurobiological substrates of dementia in the oldest-old could unmask core physiological and molecular substrates of dementia that may be otherwise overshadowed by NP and NFT neuropathological features in younger persons. Irrespective of speculations, it is clear that our current knowledge of the substrates of dementia in the oldest-old is rudimentary at best and that much more research will be required to address the cognitive health needs of this rapidly growing segment of the population.

Figure 2. Fold change in neurofibrillary tangle (NFT) (A) and neuritic plaque (NP) (B) density in cognitively intact (clinical dementia rating [CDR]=0) vs questionably impaired (CDR 0.5) subjects in representative brain regions as a function of age grouping.

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