Clinicopathologic Correlations in a Large Alzheimer Disease Center Autopsy Cohort: Neuritic Plaques and Neurofibrillary Tangles “Do Count” When Staging Disease Severity

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INTRODUCTION
Neurofibrillary tangles (NFTs) and neuritic amyloid plaques (NPs) were described by Alois Alzheimer (1) over a century ago and remain the pathologic hallmarks of Alzheimer disease (AD) (Fig. 1). NFTs are argyrophilic inclusions composed of filamentous tau protein aggregates. NPs are extracellular amyloid deposits invested by swollen, degenerating neurites. Fibrillar polymers of the Aβ peptide comprise the structural core of NPs.

AD is for all practical purposes unique to humans. Hence, careful clinicopathologic research must guide experimental models and potential therapies. Many hypotheses have been put forward to explain the biologic basis for AD. These hypotheses tend to incorporate the development of NPs and NFTs; however, in AD brain there often are many abnormalities present in addition to NFTs and NPs. Furthermore, prior studies on the correlation of NFTs and NPs to cognitive deterioration in AD have yielded somewhat differing results (see Discussion). For these reasons, some researchers have suggested recently that NFTs and NPs may contribute only marginally to dementia (2–8), or that NFTs and NPs are less relevant to cognitive decline in older patients with AD than other pathologic processes (9, 10). These seemingly contradictory results and hypotheses have produced uncertainty in the research and clinical communities about how the severity of cognitive impairment is associated with the pathognomonic features of the disease.

Linking premortem cognitive measures with postmortem neuropathology is challenging. Prospective clinicopathologic correlations require recruiting and evaluating patients over many years, during which time the parameters of evaluation must remain detailed and consistent. Ideally, each patient should be evaluated proximal to death to relate the degree of cognitive impairment to the neuropathologic features found at autopsy. In addition, technical variables often confound the assessment of NFTs and NPs in situ. Standard neuropathologic metrics for NFTs and NPs (Braak staging, Consortium to Establish a Registry for Alzheimer’s Disease [CERAD], and National Institute on Aging-Reagan criteria) (11–16) are only semiquantitative, thereby further limiting our ability to make accurate correlations of antemortem cognitive status and the severity of neuropathologic findings. Confounding disease...
**Materials and Methods**

**Subjects**

Research protocols were approved by the UK Internal Review Board. The details of UK ADC inclusion criteria, recruitment, and mental status testing have been described previously (17). Briefly, this group of older adults was recruited originally by letter and telephone contact from a volunteer pool of approximately 4,000 individuals maintained by the UK Sanders-Brown Center on Aging. This volunteer pool initially was developed from a list of registered voters aged 60 years and older in the Lexington, KY area. Other volunteers were then recruited through local media coverage of the research activities of the UK ADC and from personal referrals by individuals already enrolled in the project. The inclusion criteria for this project (on enrollment) were 1) absence of National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association criteria for AD (18), 2) absence of medical and psychiatric conditions that affect cognition and age older than 60 years, 3) initial mental status examination scores above standard clinical cutpoints for dementia (e.g. Mini-Mental State Examination [MMSE]) (18), 4) willingness to complete annual mental status examinations, and 5) brain donation at death. The assessment of cognition in these volunteers was completed on an annual basis. Tests of cognition were selected to provide data that would be comparable to those of other ADC projects. All of the subjects without dementia in this study were contacted at 6-month intervals, had detailed annual mental status testing, and had neurologic and physical examinations at least biannually. Since 2005, all subjects have had annual neuropsychologic testing and physical and neurologic examinations. The subjects in this report had been followed for at least 2 years and most for more than 10 years. Any patient who developed dementia continued to receive annual mental status testing and neurologic examinations.

**Mental Status Testing**

The extensive mental status testing of our subjects has been described previously (17). The present study focuses on the MMSE conducted closest to the date of death as the “severity metric” for analyses related to the extensive pathologic data presented. The MMSE was chosen as it was the most consistently available measure obtained from both normal subjects and subjects with dementia over the course of their evaluations.

**Pathologic Assessments**

The gross neuropathologic evaluation was carried out at the time of autopsy. Left hemisphere specimens were taken from the following neocortical regions: frontal pole (Brodman area 10), middle frontal gyrus (MFG) (area 9), superior and middle temporal gyri (SMT) (areas 21 and 22), temporal pole (area 38), inferior parietal lobule (IPL) (areas 39 and 40), occipital lobe including the primary visual area (Occ) (areas 17 and 18), anterior cingulate gyrus (area 24), and posterior cingulate gyrus (area 23). Specimens were also taken from the olfactory bulbs, hippocampus at the level of the lateral geniculate nucleus, entorhinal cortex, ambient gyrus, gyrus rectus, amygdala, basal ganglia, nucleus basalis of Meynert, thalamus, midbrain, pons, medulla, cerebellum, and choroid plexus. The specimens were immediately fixed in 10% formaldehyde, and selected specimens were fixed in 4% paraformaldehyde. Most of the specimens described were also sampled from the right hemisphere. Care was taken to evaluate any area suspicious for infarct. A total of at least 25 sections were taken from each brain. All specimens were processed in the standard manner (13), and sections were cut at 8-μm thickness. Sections were stained with hematoxylin and eosin and the modified
Bielschowsky method. The Gallyas stain was used on sections of the entorhinal cortex, hippocampus, and amygdala. If AGs or AG-like pathology were found with the Gallyas stain in ventromedial temporal lobe structures, this stain was then used on the ambient gyrus, insula, gyrus rectus, and anterior cingulate gyrus to search for AGs. All sections of cortical and ventromedial temporal lobe structures were immunostained with monoclonal antibody NCL-β-amyloid (Novocastra, Newcastle, UK) for β-amyloid peptide, and the amygdala, medulla, and olfactory bulb were immunostained for α-synuclein (Novocastra). β-Amyloid immunohistochemistry was performed after formic acid and pepsin (Biomed, Foster City, CA) pretreatment. α-Synuclein immunohistochemistry was performed after antigen retrieval at pH 8.0 (Cell Marque, Rocklin, CA) in a Decloaking Chamber (Biocare Medical, Concord, CA). Secondary antibodies were from Vector Laboratories (Burlingame, CA), including the ABC Standard Elite kit. If LBs or Lewy neurites were found in any of these sections or in the midbrain or pons, α-synuclein immunostaining was performed on neocortical, entorhinal, and hippocampal sections.

As described previously (17), comparison of the modified Bielschowsky-impregnated sections and the Gallyas-stained sections in ventromedial temporal lobe structures revealed that the Gallyas stain detected more NFTs; however, this result reached statistical significance only in the entorhinal cortex for those cases. Thus, we did not use the Gallyas stain to quantify NFTs in the isocortical structures. Senile plaques were counted using a 10× objective (field size, 2.35 mm²) in the 5 most involved fields in each section of the regions described earlier. Plaque counts were “capped” at 250 for each area. The most severely affected fields were determined by studying the whole section and marking it. Senile plaques were separated into DPs (plaques without neurites) and NPs (plaques with degenerating neurites) in each region. NFTs, DPs, and NPs were counted using Bielschowsky-impregnated sections of the MFG, SMT, IPL, and Occ, and the Gallyas-stained sections were used to count amygdala, hippocampus, and entorhinal cortex. NFTs were counted with a 20× objective (field size, 0.586 mm²) in the 5 most severely affected fields of each section of the regions described earlier. An arithmetic mean was calculated from the count of the 5 most involved fields for DPs (number of DPs per 2.35 mm²), NPs (number of NPs per 2.35 mm²), and NFTs (number of NFTs per 0.586 mm²) for each region.

Groups With and Without Non-AD Pathology

All patients with subcortical or cortical infarct(s), cortical LBs, HS, AGs, and/or frontotemporal dementia (FTD) were assigned to Group II (with non-AD pathology); patients lacking these pathologic features were assigned to Group I. The following criteria were used in this division. Because cerebral amyloid angiopathy (CAA) does not apparently contribute to dementia independently of AD or without frank infarcts (19), CAA (however advanced) was not used as a separate criterion for non-AD pathology in the absence of discrete (>1 mm) infarcts or white matter rarefaction. However, when microinfarcts were identified the patient was assigned to Group II. The diagnoses of infarcts and HS were dependent on the neuropathologic final diagnosis reports as
in prior studies (20, 21). Otherwise the criteria for non-AD pathology were as follows: the presence of any α-synuclein-immunoreactive LBs outside of amygdala constituted “cortical LBs,” and a case was designated “FTD” if it was a non-AD tauopathy (e.g. Pick disease, progressive supranuclear palsy, or corticobasal degeneration) or dementia lacking distinct histopathology, compatible with the consensus neuropathologic guidelines for FTDs (22). AGs were defined as described above. Excluded entirely from analyses were patients with Down syndrome, normal pressure hydrocephalus, brain infection, primary brain tumors or metastatic cancer in brain parenchyma.

For clinicopathologic correlations, the following criteria were applied for each patient in Group I. “Dementia” is defined as MMSE score of 20 or lower. The criterion for “NFTs present” is as follows: sum of the mean NFTs per 20× field for each of the 4 neocortical fields (MFG, MTG, IPL, and Occ); if the sum of the 4 means is >25 NFTs, then NFTs are termed “present” in neocortex. “NPs present” is defined as >2 areas in cerebral isocortex (MFG, SMT, IPL, and Occ) in which there are >10 NPs counted per 20× field.

Analysis

Consecutive subjects were evaluated from a database of patients (n = 438) followed at the UK ADC. After subjects were excluded on the basis of the above criteria, 390 subjects remained for analysis. Patients were separated into Group I or Group II according to whether or not the brain showed evidence of important non-AD neuropathology as defined above (Fig. 2). In descending order of frequency, the non-AD neuropathology consisted of infarcts (n = 167), cortical LBs (n = 64), HS (n = 28), AG (n = 23), and FTD (n = 11). Slightly less than two-thirds of patients were assigned to Group II. Seventy-six subjects (19% of total cohort) had more than 2 non-AD pathologies.

Ordinary least-squares regression was conducted to assess the relationship between MMSE and NFTs, NPs, and DPs and with NFTs, NPs, and DPs predicting MMSE scores. Age-stratified analyses were also conducted. Group comparisons involved paired t-tests or analysis of variance for mean differences, and χ² analyses for frequencies. Statistical analyses were conducted using SAS 9.1 and MS Excel.

RESULTS

Groups I and II did not differ significantly with regard to demographics (Table 1) except for the MMSE scores closest to death for which Group II was lower (p < 0.01). Apolipoprotein E (ApoE) allele frequencies for Group I (n = 250 alleles tested) were 5% for ApoE2 allele, 75% for ApoE3 allele, and 20% for ApoE4 allele. For group II (n = 450 alleles tested), the ApoE allele frequencies were 7% for ApoE2 allele, 68% for ApoE3 allele, and 25% for ApoE4 allele.

### Table 1. Cohort Demographics

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Gender F/M (Ratio)</th>
<th>Mean Age (years)</th>
<th>Mean Education (years)</th>
<th>Mean MMSE (Last Evaluation)</th>
<th>Median Months Between Last MMSE, Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (No cortical LBs, AGs, HS, infarcts, or FTD)</td>
<td>134</td>
<td>83.51 (1.63)</td>
<td>82.8</td>
<td>14.7</td>
<td>20.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Group II (includes cortical LBs, AGs, HS, infarcts, and/or FTD)</td>
<td>256</td>
<td>153.103 (1.49)</td>
<td>83.1</td>
<td>15.0</td>
<td>17.7</td>
<td>12.0</td>
</tr>
<tr>
<td>p value for difference</td>
<td>N/A</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.003</td>
<td>NS</td>
</tr>
</tbody>
</table>

MMSE, Mini-Mental State Examination; LB, Lewy body; AGs, argyrophilic grains; HS, hippocampal sclerosis; FTD, frontotemporal dementia. N/A, not applicable; NS, not significant.

**FIGURE 3.** Patients with impaired cognition and findings of Alzheimer disease (AD) only have more neurofibrillary tangles (combined counts from superior and middle temporal gyri, middle frontal gyrus, inferior parietal lobule, and occipital lobe including the primary visual area) than cohorts with similar levels of cognitive function and concurrent non-AD pathologic findings (Group II). Patients are grouped according to MMSE scores. Blue bars represent Group I no Lewy bodies (LBs), argyrophilic grains (AGs), infarct(s), hippocampal sclerosis (HS), or frontotemporal dementia (FTD). The red bars and yellow bars refer to all Group II cases with cortical LBs or infarct(s), respectively. Results of 2-tailed, 2-sample Student t-test: *, p < 0.05; ***, p < 0.001.
FIGURE 4. Correlating histopathologic lesions of Alzheimer disease (AD) with premortem cognitive decline as quantified with the Mini-Mental State Examination (MMSE). (A, B) Results for neurofibrillary tangles (NFTs), (C, D) results for neuritic amyloid plaques (NPs), and (E, F) results for diffuse plaques (DPs) in Group I (A, C, E) and Group II (with Lewy bodies, argyrophilic grains, infarcts, hippocampal sclerosis, and/or frontotemporal dementia) (B, D, F). Note that the correlation coefficients are consistently higher for Group I versus Group II, and for both groups the correlation coefficients are NFTs > NPs > DPs. There are a few Group I patients with dementia who lack NFTs and NPs. SMT, superior and middle temporal gyri; MFG, middle frontal gyrus; IPL, inferior parietal lobule; PrV, primary visual cortex.

TABLE 2. $R^2$ Correlation Coefficients

<table>
<thead>
<tr>
<th>Patient Age (years)</th>
<th>Complete Cohort</th>
<th>Group I only (no cortical LBs, AGs, HS, infarcts, or EID)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>NFTs</td>
</tr>
<tr>
<td>&lt;70</td>
<td>36</td>
<td>0.12</td>
</tr>
<tr>
<td>70s</td>
<td>73</td>
<td>0.60</td>
</tr>
<tr>
<td>80s</td>
<td>196</td>
<td>0.41</td>
</tr>
<tr>
<td>&gt;90</td>
<td>85</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Mini-Mental State Examination versus neurofibrillary tangles (NFTs), neuritic amyloid plaques (NPs), and diffuse plaques (DPs) stratified by age. AGs, argyrophilic grains.
TABLE 3. $R^2$ Correlation Coefficients for Group I

<table>
<thead>
<tr>
<th>Neuroanatomical Area or Grouping</th>
<th>MMSE vs NFT</th>
<th>$R^2$ counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entorhinal cortex</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Hippocampus (CA1)</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Hippocampus (subiculum)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Summed counts, mesial temporal cortical structures</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Superior and middle temporal gyrus</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Summed counts, isocortical structures</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

Mini-Mental State Examination (MMSE) versus neurofibrillary tangle (NFT) counts in different areas of human brain (individual areas or summed counts).

allele. These frequencies were not significantly different by group ($\chi^2; p = 0.16$).

The impact of the presence of non-AD pathology is shown in Figure 3. NFT counts were stratified by MMSE scores. NFT counts in brains with either infarct(s) or cortical LBs showed significantly lower mean NFT counts relative to patients with comparable dementia with AD only. We then assessed the relationship between NFTs, NPs, and DPs, and MMSE in Group I and Group II patients using regression analyses (Fig. 4). The best pathologic predictor of MMSE was NFTs in Group I ($R^2$ correlation coefficient ~0.73). In contrast, $R^2$ for the regression of MMSE versus NFTs in Group II was ~0.31. $R^2$ was lower for NPs and DPs, but as with NFTs the fit was better in Group I than for Group II. Separating Group I from Group II improved the $R^2$ coefficient for predicting MMSE with NFTs, NPs, and DPs, regardless of the patient’s age group, and the general pattern of $R^2$ coefficients (NFTs > NPs > DPs) remained fairly constant across all the age groups (Table 2). Results were not significantly altered when the MMSE was adjusted to account for the time from the last test administration to death (data not shown). To address whether the isocortical areas were the best neuroanatomical regions in which to correlate the presence of NFTs with MMSE, we compared the $R^2$ coefficients for NFT counts versus antemortem MMSE scores for different areas of cerebral cortex (Table 3). The results show that for mesial temporal lobe structures, either in isolation or summed together, NFT counts are consistently poorer for predicting MMSE scores than isocortical structures.

Group I and Group II differed in the proportion of patients with a MMSE score of 30 (no evidence of dementia by MMSE): 16% of Group I (n = 22) versus 5% for Group II (n = 13). To determine whether these cases constituted a confound that biased Group I to have a better correlation between MMSE and NFTs, we also performed the regressions of MMSE versus NFTs on Group I cases omitting all patients with MMSE = 30. After dropping these cases from analysis, the $R^2$ value for the association between Group I NFTs and MMSE was still 0.71. Of patients with MMSE $\geq$28, 47 were in Group II. Most of these (33) had cerebral infarct(s); however, 11 had AG.

We also evaluated Group I patients with CAA or amygdala LBs to determine whether eliminating these groups from Group I increased the correlation between MMSE and AD pathology. This would be expected if CAA or amygdala LBs were associated with lower MMSE for a given amount of AD pathology. When these cases (n = 34) were removed from Group I, the Group I $R^2$ values increased for NFTs (0.80) but decreased for NPs (0.57) and for DPs (0.29).

Because prior research has indicated that distinct patterns of AD-related pathology are observed in patients of different age groups (4, 9), the data were stratified to determine whether there were important differences between age groups in the neuropathology of patients in Group II (Table 4). The data show that the types of non-AD pathology changed according to age. Patients who died younger had a higher likelihood of FTD and a lower likelihood of infarcts or AG. The overall proportion of patients in Group II trended higher in older patients with patients older than 90 years being almost 70% in Group II. Within Group II, more than three-quarters (76%) of the oldest patients (age 90+ years) had CVD and almost one-quarter (24%) of these patients had more than 1 type of non-AD neuropathology.

Clinicopathologic Correlation in a Theoretical Context

By identifying a group of patients who lacked superimposed neurodegenerative and CVDs (which includes some patients with NPs and NFTs but without dementia), we have the opportunity to examine the hypothesis that NPs and NFTs contribute to cognitive decline in AD. As demonstrated in Figure 5, our data show that most patients either do not have dementia and NPs and NFTs (41.8%) or have dementia with abundant NPs and NFTs (32.8%). However, most cases outside of those 2 groups (>20%) are likely to represent patients with “subclinical” disease that are theoretically highly likely to be represented in any sample of aged brains.

DISCUSSION

The goal of this study was to use a well-characterized clinical cohort to assess how aged persons’ premortem...
cognitive status (severity) was associated with postmortem counts of NPs and NFTs. The results show strong relationships between AD pathology (NFTs > NPs > DPs) and the extent of premortem cognitive decline. This association held for each age group as long as patients with appreciable non-AD pathology were excluded. The pattern of pathology observed in this sample of patients with and without dementia is highly compatible with the prevalent hypothesis of AD pathogenesis (23, 24).

Clinicopathologic correlation in the context of the aged brain is difficult. There are some limitations to our study to consider. First, we used the MMSE as the sole indicator of cognitive ability. Other measures may be more sensitive and specific for early cognitive decline, because they exhibit fewer ceiling or floor effects (17, 18, 25). However, the use of the MMSE allows our results to be interpreted in the context of other existing clinicopathologic cohort databases that have relied on the MMSE for cross-study comparisons (26–30). Also, using the MMSE as a metric for disease severity allows continued assessment of disease progression over time. Our analyses are not able to account fully for subtle cognitive changes of mild cognitive impairment that may be clinically relevant yet poorly understood. Second, unavoidable ascertainment bias exists in the UK ADC cohort. This cohort represents a convenience sample rather than an

FIGURE 5. Clinical and pathologic data are assessed in the context of prevalent hypotheses about the pathogenesis of Alzheimer disease (AD). (A) The amyloid cascade hypothesis is that genetic and environmental influences contribute to the formation of neuritic amyloid plaques (NPs), which in turn potentiate neurofibrillary tangle (NFT) formation, and together, NFTs and NPs contribute to the synapse elimination and cell death seen in AD. (B) The chart relates the clinical features of AD to the pathology. As NPs and NFTs accumulate and cognition deteriorates there is a time during which no overt dementia is detectable. (C) A simple chart to evaluate whether the hypotheses about AD pathogenesis are borne out by clinicopathologic correlation. (D) It would be counter to the hypotheses in A and B, if the table positions in C designated w, x, y, and z were highly represented in the population. (E) Empirical data from Group I patients are highly compatible with the hypothesis shown in A and B, because the vast majority of patients either have no dementia with no pathology (~42%), have dementia with NPs and NFTs (~33%), or are in some transitional condition (~20%).
epidemiologic cohort. Sample demographic biases include a relatively advanced age at death (mean >80 years), gender bias (ratio of female to male of 3:2), and advanced educational level (~15 years). Patients with neurodegenerative diseases tend not to die in nondementia or “transitional” phases, so there is under-representation of more cognitively intact patients (25, 31). Of the 390 patients reported in this study, however, 123 had MMSE scores of 28 or higher. Hence, patients without dementia were relatively well represented in this study. Furthermore, as shown in Table 1, Group I and Group II subjects showed nearly identical age, sex, time since last MMSE, and educational parameters. A third potential limitation of this study involves the difficulties inherent to quantifying neuropathologic lesions in neurodegenerative diseases (12, 32). These methods have been published previously and used for productive studies in AD (17). Consensus diagnostic guidelines (13, 33) recommend semiquantitative methods rather than lesion counts because these are less laborious with satisfactory inter-rater reliability when counts between different laboratories are compared (12, 14, 34). However, if performed consistently, counts of NFTs, NPs, and DPs produce a more finely graded readout that can be linked to other clinical and pathologic variables.

The Group I/Group II assignment criteria do not fully address the many changes present in aged human brains. Disease processes other than cerebral infarcts, dementia with LBs, AGis, FTDS, and HS occur in many aged persons. For example, brain pathology and clinical dementia are associated with psychiatric illness, heart surgery, alcoholism/substance abuse, diabetes, and other metabolic disorders (30, 35). Patients from each of these groups were present in Group I. In the future, more refined clinicopathologic correlation may show an even greater correlation between NFTs and NPs and the development of AD.

Although cases with non-AD pathology (Group II) were separated for clinicopathologic correlation, this separation does not imply that AD-related pathology is absent from Group II cases. In fact, the results shown in Figure 4 suggest that NFTs and NPs do contribute to cognitive decline in many Group II cases.

Because clinicopathologic correlation is important for diseases without natural animal models, prior researchers have also attempted to assess critically the correlation of NFTs/NPs and cognitive decline in AD. The ground-breaking studies correlating AD neuropathology with antemortem clinical decline area were performed by Tomlinson, Blessed, and Roth in the 1960s (36, 37). However, these studies were performed before the importance of other neurodegenerative diseases (e.g., synucleinopathies, many FTDS including tauopathies, and argyrophilic grain disease) was appreciated.

Our results indicate that the number of NFTs in cerebral isocortex correlates best with AD cognitive decline. The contradistinction between isocortical and allocortical (mesial temporal lobe) pathology is important. In the first place, NFTs are seen relatively frequently in the entorhinal cortex, hippocampus, and amygdala of aged persons without dementia (18, 38–40). But just as important, data from a number of prior studies show evidence of a nonlinear “ceiling effect” relationship between dementia and the number of NFTs in medial temporal structures in the later stages of AD (39, 41–45). The late AD plateau of NFT densities may indicate that there is turnover of NFTs in, for example, the entorhinal cortex in late-stage AD. Unfortunately, it is impossible to either prove or disprove this hypothesis in humans at this time. Yet there is a discrepancy worth noting: the hippocampus, amygdala, and entorhinal cortex are anatomical areas associated with the pathology of AD, although these medial temporal structures are not where neuropathology correlates best with dementia at any stage of the disease.

Numerous studies have shown that isocortical NFT numbers correlate relatively well with clinical dementia severity (11, 16, 17, 26, 27, 46–54). Some of these studies are hampered by semiquantitative metrics of dementia, pathology, or both. For example, when neurofibrillary pathology is stratified by Braak and Braak staging, there are only 3 stages (Braak stages IV, V, and VI) that encompass the progression of neurofibrillary pathology in the cerebral isocortex. Braak and Braak stages correlate satisfactorily with clinical dementia levels (15, 54); however, quantitative counts provide a more textured clinicopathologic correlation. Most prior studies have shown a relatively poor correlation of amyloid plaques to dementia (18, 26, 27, 46–49, 52, 55–57; however, see also 58, 59). The general pattern of “noncorrelation” is that aged brains can sustain numerous isocortical NPs and (fewer) NFTs with negligible apparent deficits or only a mild loss of episodic memory (24, 38). A substantial subgroup of “plaque only” AD (60) has not been borne out by large clinicopathologic studies, and there is not such a group in our series.

Although NP counts correlate less well than NFTs with dementia severity, these data do not necessarily argue against the central importance of NPs in the disease process. The data can best be interpreted to imply that AD pathology does not begin to diminish cognitive reserve until both NPs and NFTs are prevalent in isocortex. Prior studies have also shown evidence that NPs may mediate their effect via NFT formation (52). The manner in which pathology and dementia correlate in AD brains in no way proves, but is absolutely compatible with, the most prevalent scientific hypothesis about AD pathogenesis, the “amyloid cascade hypothesis” (23). According to this hypothesis, primary genetic and/or environmental factors contribute to overproduction of “toxic” plaque amyloid, which then leads to neurofibrillary pathology. Together, NPs and NFTs may contribute to the cell loss and synapse elimination that culminate in dementia. The amyloid cascade hypothesis is supported by data derived from genetics, animal models, and cell culture studies (24); however, the compatibility of neuropathologic data has been debated (61). Our data are incorporated into a theoretical framework and presented in Figure 5. In the progression of the amyloid cascade hypothesis, a significant minority of aged persons without dementia are predicted to harbor isocortical NPs and some NFTs. Hence, the theory and the data are compatible with each other.

Complementing the clinicopathologic correlation, our data underscore the point that it is impossible to study AD pathology without rigorous assessment of other prevalent types of neurodegeneration in the aged brain. The relationships of AD pathology and vascular pathology to dementia
in older persons have been investigated (20, 40, 62–64), but currently no validated, overarching qualitative or quantitative classification system for vascular brain pathology provides precise clinicopathologic correlations. However, when older patients with brain vascular pathology are grouped together, they usually exhibit a relatively rapid progression of dementia (21, 28, 65, 66), and AD lesions are less severe for a given extent of dementia (67–69). Notwithstanding the common risks associated with the ApoE4 polymorphism, vascular risk and AD risk are apparently independent (20, 70–72). From a practical standpoint, the presence of any brain infarct—even subcortical infarcts or microvascular disease—increases the amount of expected premortem dementia (21, 28, 66, 73, 74), so correlations of AD pathology with dementia must include careful neuropathologic analyses of the entire brain.

CVD may be an important variable in the controversy about whether or not AD pathology in the “oldest old” persons has a different relationship to dementia in comparison to persons who died at a younger age (9, 10). Of persons who die aged >90 years old, 50% to 85% can be expected to show appreciable CVD (68, 75, 76). However, in the current and prior studies (15), the correlation of AD histopathology with dementia was the same in Group I patients from all age categories. There is a need for better clinicopathologic assessment scales to grade CVD contributions to dementia (77), and further work remains to be performed in this area.

In addition to cases with CVD, we removed from Group I cases with cortical LBs, AGs, HS, or FTD. Prior studies have shown that these subtypes of pathology are quite common in aged brains (78–80). LBs are considered “incidental” if present in AD amygdala only (81–84); therefore, cases with LBs in the amygdala only were assigned to Group I for this study. However, for the current study, the $R^2$ correlation coefficient for NFTs versus MMSE improved from 0.73 to 0.80 when cases with amygdala LBs and CAA (total n = 34) were removed from Group I. This indicates that amygdala LBs and/or CAA may, even without the presence of other CVD, alter the correlation of AD pathology with dementia severity.

In summary, this study helps to solidify 3 important points about the connection between AD pathology and premortem cognitive decline: first, to evaluate AD pathology one must carefully exclude or control inclusion of brains with prevalent concomitant pathology; second, the numbers of isocortical NFTs and NPs correlate well with premortem cognitive decline; and last, careful clinicopathologic correlation supports the prevalent model of AD pathogenesis. Although none of these “prove” directly a causal connection, it is important to conceptualize that clinicopathologic correlation in AD supports the importance of NFTs and NPs in the clinicobiologic sense. Until better surrogate biologic markers of AD are discovered, refined, and proved, plaques and tangles will remain the sine qua non of AD.

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