
Analyzing 1,677 cases with antemortem diagnosis of dementia from the National Alzheimer’s Coordination Registry, Nelson et al (1) recently commented on the cases that fall outside the National Institute on Aging and Reagan Institute recommendations. Of the cases, 82.4% fell into diagnostic “boxes” within the rubric of the consensus recommendations. Two specific categories were considered: 1) “tangle-intensive” cases, with the highest density of neurofibrillary tangles but only moderate density of neuritic plaques (9.4% of the overall). These cases were considered more likely to be designated as “high likelihood” that dementia was due to Alzheimer disease (AD); whereas 2) “plaque-intensive” patients with high density of amyloid plaques and intermediary severity tangles (6.0% of total) were typically designated as “intermediate likelihood.” Unfortunately, both of these categories are not identical with the “tangle-dominant” type (with 3- and 4-repeat tau pathology similar to neurofibrillary tangles in “classic” AD but often restricted to the limbic system, absence of neuritic plaques, and no or very little amyloidosis), accounting for 5% to 7% of oldest-old subjects with dementia (2), and the “plaque-predominant” type with abundant amyloid plaques, no or very little neuritic pathology restricted to the limbic system, and lacking overt tangle formation, accounting for 3.5% to 8% of subjects with dementia aged 85 years or older (3). Their plaque-intensive type is probably similar to the “hippocampal” type of AD (neuritic Braak stages III/IV) with frequent neuritic plaques.

Among 1,700 elderly persons with dementia (mean age, 84.3 ± 6.0 years; 90% aged >70 years), AD pathological diagnosis was present in 80%, “pure” AD (Braak stages V/VI) was present only in 36.9%, whereas 8.8% were “atypical” forms; AD and other pathological findings were present in 37.3%, indicating the frequency of “mixed pathological findings” in aged patients (4). Another difference between the data of Nelson et al (1) and our personal experience concerns the final Mini-Mental State Examination scores in various “atypical” cases of dementia. For the tangle-intensive cases (Braak stage VI) encompassing 1.3% of their cohort with dementia, the final Mini-Mental State Examination scores seemed to approximate those of severe AD (1), but the severity of cognitive dysfunction in tangle-dominant dementia patients was less than that of “classical” AD (mean, 9.0 vs 2.0) (2). Furthermore, the statement suggesting that cases Nelson et al designated as plaque-intensive and tangle-intensive cases all belong to the category of intermediate likelihood for AD (3) is not correct because the plaque-predominant and tangle-dominant dementia types obviously were different from those designated by Nelson et al. Nevertheless, Nelson et al correctly concluded that more exact categories, consideration of frequent “mixed pathological findings” in aged persons, and a better understanding of the pathological findings of early phases of the disease might be helpful for guiding neuropathologists in the diagnosis of AD.

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REFERENCES
1. Nelson PT, Kukull WA, Frosch MP. Thinking outside the box: Alzheimer-type neuropathology that does not map directly onto current consensus recommendations. J Neuropathol Exp Neurol 2010;69:449–54

Authors’ Reply:
We were glad to read the letter by Dr Kurt Jellinger on topics related to our recent article about cases falling outside the National Institute on Aging and Reagan Institute recommendations. For the sake of this article, our categorical “labels” pertained directly to the diagnostic grid of CERAD scores and Braak staging (Fig. 1 in [1]). As Dr Jellinger mentioned, these labels overlap with some existing terms with other connotations. Because our analysis was drawn from the National Alzheimer’s Coordinating Center’s data set, those cases felt by the submitting neuropathologist to fall into “tangle-dominant dementia” were mostly excluded from this analysis.

It has been observed previously that there are differences between studies in the final Mini-Mental State Examination scores even for “classic” AD patients with given Braak stages (2). We note that a similar grid of CERAD scores and Braak staging appears in Table 2 of the cited article by Dr Jellinger (3), and for both Braak V/VI + CERAD “moderate” and Braak III/IV + CERAD “frequent” cases, the diagnosis of “intermediate likelihood” is suggested in the table.

We appreciate and agree with Dr Jellinger’s other points, particularly regarding the interpretation of cases with multiple disease processes. It is possible that the submitting neuropathologists included the presence or absence of cerebrovascular disease into their interpretation of the likelihood of AD as the primary cause of a subject’s cognitive impairment. Our study did not seek to address this issue. It would be difficult to examine the interaction of these pathologic findings in the mind of the neuropathologist and harder still to determine the mechanistic links in the brains of our subjects. Nonetheless, we agree that better understanding of these prevalent disease combinations...