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Journal Club: Comparison of symptomatic and asymptomatic persons with Alzheimer disease neuropathology

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Advances in neuroimaging, biomarkers, and clinical data have led to the hypothesis that the pathologic process of Alzheimer dementia begins decades prior to functional decline and diagnosis.[1–3] High-profile clinical trial results have shown that biomarker changes can be made via pharmacologic intervention; however, the timing of this intervention has likely been too late to affect the cascade of neurodegenerative changes.[4,5] In "Comparison of symptomatic and asymptomatic persons with Alzheimer disease neuropathology" by Monsell et al.,[6] neuropathologic and clinical data were used to determine the risk of developing clinically significant cognitive impairment. This work represents a significant contribution because it examines a large cohort of autopsy data, which includes patients with Alzheimer dementia neuropathology who were clinically normal or diagnosed with mild cognitive impairment and Alzheimer-type dementia. The authors report a 3-fold increase in the risk of cognitive symptoms in association with quantifiable increases in neurofibrillary tangle pathology. In addition, several other factors, including *APOE* gene status, history of depression, and age, affected the clinical presentation. The ultimate goal of this investigation and similar studies is to facilitate the early and accurate identification of those at risk of developing Alzheimer dementia such that potentially disease-modifying therapies may be considered.

HYPOTHESIS AND DESIGN The authors hypothesized that there may be specific demographic, clinical, or neuropathologic features that are associated with clinical impairment consistent with a diagnosis of Alzheimer dementia in a group of patients with known Alzheimer dementia neuropathology at autopsy. The study design is case-control with symptomatic dementia as the disease state of interest.

METHODS The data used for this study were extracted from the National Alzheimer's Coordinating Center Uniform Data Set and Neuropathology Data Set, which included 1,775 patients who underwent autopsy from 2005 to 2012. Only patients who had a clinical follow-up visit to one of the database centers in the year prior to death were included. Other inclusion criteria required the presence of both diffuse plaques and neuritic plaques on pathologic examination. This is important because it excluded subjects with no Alzheimer dementia pathology and also created a "control" group that was asymptomatic clinically yet had neuropathologic changes consistent with Alzheimer dementia. These parameters yielded 906 patients. This approach was derived from the National Institute on Aging–Alzheimer's Association (NIA-AA) guidelines for the neuropathologic assessment of Alzheimer dementia,[7] which propose the grading of Alzheimer dementia into 4 ranges (not, low, intermediate, high) based on the "ABC" score (A: Thal phase for Aβ amyloid plaques; B: Braak stage for neurofibrillary tangles; and C: Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque frequency). Notably, Thal phase (the anatomical distribution of amyloid plaques) was not available in the datasets used for this study; however, the inclusion criteria were designed to permit analysis of the largest number of subjects with Alzheimer disease (AD) pathology, given this limitation.

The determination of symptomatic disease was based on the Clinical Dementia Rating scale (CDR), a validated tool that evaluates 6 functional domains and categorizes subjects' dementia as none, questionable/very mild, mild, moderate, or severe.[8] In this study, any classification greater than "none" (CDR $\geq$ 0.5) was considered symptomatic. The degree of pathologic changes and other clinical characteristics were then evaluated using logistic regression models (first bivariate, then multivariate) to look for associations with the clinical symptomatology. The results of these analyses are the odds ratios (ORs) of factors that lead to clinically symptomatic dementia based on a cohort of patients with neuropathologic changes consistent with Alzheimer dementia.

RESULTS Demographic data reveal that the cohort was 95% white, 45% female, 41% aged 80–89 years, 70% college-educated, and 49% had at least 1 *APOE* ε4 allele. The asymptomatic group included 82

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subjects, which represents only 9% of the total. The authors point out that the asymptomatic population is slightly older (mean 86.2 years vs 81.3). Also, 52.2% of symptomatic patients had at least 1 *APOE* ε4 allele, compared to 16.2% of the asymptomatic group. Neuropathologically, asymptomatic individuals were more likely to have low B (neurofibrillary tangles) and low C (neuritic plaques) scores (77%), and 50% of the symptomatic group had both high B and high C scores. In multivariate logistic regression, the only factors that reached statistical significance in asymptomatic subjects were older age, lower Hachinski ischemic score, lack of *APOE* ε4 allele, and lower B score.

INTERPRETATION The authors sought to elucidate risk factors that were associated with clinically symptomatic Alzheimer dementia in those with known Alzheimer dementia pathology. The design of this work in the form of a case-control study is appropriate to address the authors' goals. Ideally the question that the authors pose would be addressed by a prospective cohort study, which follows patients from asymptomatic enrollment until death; however, the logistics and timing of such a study would likely be prohibitive at present. One of the primary strengths of the study is the number of patients with identified Alzheimer dementia pathology via the current diagnostic gold standard, postmortem neuropathologic examination. However, the number of patients should be considered in the context of an expected effect size for this study, which was not reported. The weaknesses of the study lie mainly in limitations of the available dataset. First, attempting to apply the NIA-AA guidelines to the data is not perfect, as a Thal phase for Aβ plaques was not available. According to the guidelines, the simplest way to include all patients with Alzheimer dementia pathology is to include all patients with at least Thal phase 1 (i.e., an ABC score of 1, X, X eliminates all "not" Alzheimer dementia neuropathology). The C score of 1 or higher used in this study (i.e., requiring the presence of neuritic plaques) may have excluded some patients who would have otherwise met criteria. Due to the limitations in the assessment of diffuse plaques (and missing data in this study), the scheme used by the authors likely led to the most accurate classification possible. Amyloid imaging techniques represent an emerging technology for classifying patients with Alzheimer disease (AD) pathology and may be useful for assigning Thal phase in vivo in future prospective studies.

Another major limitation of the dataset is the small "control" group, with only 9% of patients in the asymptomatic group. One possible explanation for this disparity in group sizes is a sampling bias in which patients with clinical symptoms may be more likely to consent to autopsy and to participate in AD research. Based on current hypotheses of disease progression in Alzheimer dementia and accumulating evidence of neuropathologic changes preceding symptom onset, the predicted proportion of asymptomatic subjects with Alzheimer dementia pathology would be much higher than reported in this study. Another challenge in interpreting these data is the oversimplified classification scheme of symptomatic vs asymptomatic using the CDR. Categorization via the 5 stages of the CDR or use of the CDR sum of boxes score, as opposed to a binary classification, may have been a more clinically relevant assessment of degree of impairment to correlate with risk factors.

The results of this study are presented as ORs, which can be more difficult to interpret compared to relative risk; however, ORs allow for easier adjustment of potentially confounding covariates.[9]

Vascular pathology represents a known confounding and contributing factor in the diagnosis of Alzheimer dementia. The investigators did attempt to address this complex issue by pathologically identifying the presence of large and small infarcts as well as amyloid angiopathy. In addition, the Hachinski ischemic score (HIS) was available for 79% of the cohort. In multivariate analysis, only the HIS was correlated with symptomatic Alzheimer dementia, highlighting the relationship between Alzheimer dementia and vascular pathology and the clinical significance of attending to modifiable cerebrovascular risk factors in attempts to maintain brain health.

A seemingly paradoxical observation was that older age correlated with lower risk of symptomatic disease. As the authors suggest, this finding may be the result of a healthy survivor effect and a selection bias of the control group, as persons with memory concerns or a family history of Alzheimer dementia are often compelled to enroll as normal control subjects.

Overall, the authors were able to identify several factors that were statistically significant in predicting the presence of symptomatic disease. Of particular interest, *APOE* ε4 is strongly associated with symptomatic disease even when adjustments have been made for the underlying neuropathologic changes. One could argue that based on the results of this article, *APOE* ε4 data and the Hachinski score are relatively easily obtained and may aid in the prediction of risk for developing symptomatic AD. Likewise, the importance of neurofibrillary tangles in the development of symptomatic disease is emphasized in this neuropathologic study and consistent with previous reports.[10] Development of imaging techniques specific to neurofibrillary tangles to complement currently available amyloid imaging techniques may also greatly improve the accuracy of prediction of symptomatic AD.

AUTHOR CONTRIBUTIONS

Dr. Brosch prepared the original and revised manuscripts. Dr. Matthews edited the manuscripts for content and style.

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DISCLOSURE

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