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Examination of the Clinicopathologic Continuum of Alzheimer Disease in the Autopsy Cohort of the National Alzheimer Coordinating Center

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Abstract

To test the hypothesis that Alzheimer disease (AD) is a clinical and pathologic continuum between normal aging and end-stage dementia, we selected a convenience sample of subjects from the National Alzheimer Coordinating Center 2005 to 2012 autopsy cohort (n = 2,083) with the last clinical evaluation within 2 years before autopsy and no other primary neuropathologic diagnosis. Demographic and neuropathologic characteristics were correlated with the Clinical Dementia Rating–Sum of Boxes in the 835 subjects meeting these criteria. Both neuritic plaques and neurofibrillary tangles independently predicted Clinical Dementia Rating–Sum of Boxes. Severe small-vessel disease, severe amyloid angiopathy, and hippocampal sclerosis were also independently associated with the degree of cognitive impairment. By contrast, education was a strong independent protective factor against cognitive deficits. The cause of mild to moderate dementia remained uncertain in 14% of the patients. Inverse probability weighting suggests the generalizability of these results to nonautopsied cohorts. These data indicate that plaques and tangles independently contribute to cognitive impairment, that concurrent vascular disease strongly correlates with cognitive dysfunction even in a sample selected to represent the AD pathologic continuum, and that education further modifies clinical expression. Thus, multiple concomitant etiologies of brain damage and premorbid characteristics contribute to the uncertainty of AD clinicopathologic correlations based only on tangles and plaques.

Keywords

Alzheimer disease; Cerebral amyloid angiopathy; Hippocampal sclerosis; Neuritic plaques; Neurofibrillary tangles; Small-vessel disease

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INTRODUCTION

Evidence accumulated in the past two decades has recently prompted a change in the framework for both the clinical and the pathologic diagnosis of Alzheimer disease (AD). To link the clinical continuum of cognitive decline with the AD pathologic process, the criteria for the clinical diagnosis of mild cognitive impairment (MCI) and dementia caused by AD have been refined with the incorporation of cerebrospinal fluid and imaging biomarkers of neuronal injury and amyloid deposition (1, 2). The new pathologic diagnostic criteria revise the historical view that the definite diagnosis of AD should reflect the presence of both the typical pathologic changes and a documented history of clinical dementia (3, 4). By separating the requirement for the presence of dementia during life from the neuropathologic assessment, these new criteria acknowledge that the AD pathologic process starts before the onset of cognitive deficits (5–10) and that the relationship between specific neuropathologic findings and the presence of clinical manifestations was not precisely defined by the previous set of criteria (11), may be inexact, and is, at best, probabilistic.

The relationships between the neuropathologic findings at autopsy and their clinical correlates in AD have been a matter of extensive study and debate (12). Among the factors that may complicate the interpretation of clinicopathologic correlations are 1) the need for a very large number of subjects with standardized clinical and neuropathologic evaluation to detect potentially complex relationships; 2) the existence of variable intervals between the last clinical evaluation and autopsy; 3) the frequent presence of concurrent disease processes, for which often there is no validated quantitative or staging protocol (i.e. cerebrovascular disease and other neurodegenerative diseases); and 4) potential additional effects of age group, ethnicity, sex, or occupation.

In 2005 all of the Alzheimer Disease Centers (ADCs) in the United States adopted a Uniform Data Set for the annual clinical follow-up evaluation of the subjects and a standardized protocol for the neuropathologic assessment at autopsy. We took advantage of the 2005 to 2012 autopsy cohort of the National Alzheimer Coordinating Center (NACC) to test the hypothesis that there is a pathologic continuum that parallels the clinical continuum of AD-associated cognitive decline. To examine the impact of the AD pathologic process on cognition, we excluded subjects with a non-AD primary clinical or pathologic diagnosis that could impair cognition. In addition, to minimize “noise” derived from a long time lapse between the last clinical evaluation and death, we limited our sample to those subjects who had undergone their last clinical assessment within 2 years before autopsy. We investigated the independent contribution of demographic variables (age, sex, and education) plaques and neurofibrillary tangles (NFTs) and common concurrent pathologies (i.e. small-vessel disease, Lewy bodies, etc.) to cognitive impairment, as measured by Clinical Dementia Rating Scale–Sum of Boxes (CDR-SOB), using robust multivariable regression analyses. We also tested the generalizability of the findings using inverse probability weighting methods to account for any biases related to undergoing autopsy.

MATERIALS AND METHODS

Subject Inclusion and Exclusion Criteria

Subjects were participants in a longitudinal cohort study of aging in any of the 34 past and present National Institute on Aging–funded ADCs. This multicenter study has been described in detail elsewhere (13–15). Briefly, it consists of a baseline visit and annual follow-up visits, in which a Uniform Data Set is acquired, including subject demographics and standard motor, behavioral, functional, and neuropsychologic assessments, with data residing in a centralized database. Subjects were selected from those entered in NACC database between September 2005 and September 2012 and meeting the following inclusion

criteria: 1) final clinical evaluation within 2 years before death; 2) aged 50 years or older at death; and 3) underwent autopsy and autopsy findings were consistent with a primary neuropathologic diagnosis of AD or not sufficient to establish any other primary neuropathologic diagnosis. Exclusion criteria were 1) autopsy findings consistent with a primary neuropathologic diagnosis of a disease other than AD (i.e. frontotemporal lobar degeneration [FTLD], dementia with Lewy bodies, hippocampal sclerosis, vascular dementia, prion disease, Parkinson disease, Huntington disease, hypoxia, ischemia, necrosis, hemorrhage, other non-neurodegenerative diagnosis) or 2) cognitive impairment attributable to alcohol use, depression, medication use, or medical illness. The flowchart in Figure 1 depicts the selection procedure. The 2005 to 2012 NACC autopsy cohort consists of 2,083 subjects, of whom 835 subjects met all the eligibility criteria and did not meet any of the exclusion criteria.

Data Collection

Demographic and clinical data used in this study included sex, years of education, age of death, and last CDR-SOB (16) (Table 1). For statistical analyses, the variable “age of death” was treated as a continuous variable, but the result of its effect on the CDR-SOB was expressed in 5-year units. Similarly, “years of education” was treated as a continuous variable but its effect on the CDR-SOB was expressed in 4-year intervals roughly corresponding to the education stages of high school, undergraduate college, and postcollege education. The CDR-SOB score was chosen as the outcome clinical variable because 1) it is a measure of global cognitive status that, while capturing the impact of cognitive impairment in instrumental activities of daily life, is sensitive to early stages of symptomatic AD including MCI (17, 18), and 2) unlike neuropsychologic tests, CDR is not subjected to practice effect associated with retesting because it is based on the clinician's judgment. The CDR-SOB values range from 0 to 18, with higher values indicating worse cognitive/functional status. For statistical analyses, we categorized the CDR-SOB variable in 6 intervals (0, 0.5–3, 3.5–6, 6.5–12, 12.5–17, and 18), roughly corresponding to normal; MCI; and mild, moderate, severe, and end-stage dementia, respectively. These categories were based on a preliminary inspection of the sample data and on those validated by O'Bryant et al (17, 18) in the entire 2008 NACC data set (autopsied and not autopsied). The main difference with their study is that we deliberately separated the latter category (CDR-SOB = 18) from the adjacent one (CDR-SOB = 12.5–17) to isolate the ceiling effects of CDR-SOB in end-stage dementia, which is understandably overrepresented in an autopsied cohort as compared with a living cohort. In the analysis, we treated these categories as ordered, although we did not make further assumptions on specific relationships between categories.

Neuropathologic variables included the Braak stage of NFTs (19, 20) (0, none; I–II, entorhinal; III–IV, limbic; and V–VI, isocortical), the Consortium to Establish a Registry for Alzheimer Disease (CERAD) score of neuritic plaques (21) (none/sparse, moderate, or frequent), the presence of Lewy bodies in any region, and the extent of vascular pathology (cerebral amyloid angiopathy [CAA], small- and large-vessel disease, and hippocampal sclerosis). Although the 2012 National Institute on Aging–Alzheimer Association recommendations for the diagnostic assessment of Alzheimer disease neuropathologic changes (ADNCs) (3, 4) added the Thal stages for amyloid deposition (22), these measures were not available in the NACC Neuropathology Data Set. While more objective and quantitative methods of assessment are developed and validated, NACC neuropathology guidelines recommend the use of a qualitative and subjective grading system of the overall severity (rather than an individual vessel) to assess arteriosclerosis, atherosclerosis, and CAA (none, mild, moderate, or severe). Other vascular lesions such as cortical microinfarcts or lacunar infarcts were only documented as present or absent and were not considered in this study. Hippocampal sclerosis was defined as the presence of selective neuronal loss and gliosis

("sclerosis") limited to CA1 and subiculum, with variable additional involvement of endplate, CA2, entorhinal cortex, and amygdala.

Statistics

The association of demographic and neuropathologic variables with ordered categories of CDR-SOB was examined with adjacent-categories logit models (23), with potentially different effects for different adjacent categories of CDR-SOB, using the VGAM package in R software (24) (see Supplemental Digital Content 1, http://links.lww.com/NEN/A532, for details). To assess the need for a different effect for the CDR-SOB comparison at the lowest levels, including 0, we fit a model that excluded subjects with CDR-SOB = 0. This led us to include a separate effect for Braak stage for the comparison between the lowest 2 CDR-SOB categories. The simpler model (Model 1) only included demographic variables (sex, age of death, and education). Next, the AD pathologic hallmarks, that is, CERAD score of neuritic plaques and Braak stage of NFTs, were added to the model (Model 2). In a third step, the concurrent pathologies (Lewy bodies, CAA, small- and large-vessel disease, and hippocampal sclerosis) that are routinely assessed by the neuropathologists were added to the model (Model 3 or full model).

A potential concern of autopsy studies is that their conclusions may not be generalizable to the subjects who died but did not undergo autopsy because the decision to consent for autopsy may be associated with bias. To overcome potential selection bias and to reweight back to the source population, we fit inverse probability weighted versions of the above adjacent-category models. Similar methods have been proposed and used to analyze autopsy data sets for AD clinicopathologic correlations (25, 26). The weights were the inverses of the probabilities of autopsy given death and other covariates such as sex, age of death, education, and CDR-SOB based on logistic regression models.

RESULTS

Table 1 describes the demographic characteristics of the participants at each level of cognitive function, as indicated by their CDR-SOB score proximate (≤2 years) to death. Tables 2 and 3 describe the neuropathologic findings in each of these clinical groups. Table 4 depicts a summary of the results of the multivariable regression models, with model 3 (full model) showing the independent effects of individual neuropathologic and demographic variables on the CDR-SOB outcome while adjusting for all the other variables modeled.

Effect of Demographic Variables on Cognition

The average duration between the last clinical assessment and death was less than 10 months. Fifty-five percent of the subjects were male. The cohort had a median age of death of 84 years and a relatively high education level (median, 16 years of education).

Education level and cognitive performance were significantly correlated so that a higher education level was associated with decreased odds of cognitive impairment (lower CDR-SOB) proximate to death. The effect size of the education variable was equally large in models that were not adjusted for neuropathology (Model 1) or were adjusted for neuropathologic variables (Models 2 and 3).

Age of death also had a statistically significant association with cognition, with older subjects having better cognitive function (lower CDR-SOB) for a given degree of pathologic changes. In separate analyses, we examined whether this observation might be caused by a confounding survivor bias, for example, if older individuals tended to have a shorter duration between clinical onset and death than younger individuals. We found no evidence

of correlation between age of death and disease duration (Spearman $r = -0.029$, $p = 0.49$). Moreover, the significant negative association between age of death and CDR-SOB did not change after adding disease duration to the model (not shown) and was also independent of carrying the ε4 allele of the *APOE* genotype, which is known to lower the age of onset of clinical AD dementia, or of carrying the ε2 allele, which is associated with delayed age of onset (not shown).

Neuropathologic Correlates of Cognition

Alzheimer Disease Neuropathologic Changes—Although examination of Table 2 reveals an expected positive correlation between levels of ADNCs (CERAD scores of neuritic plaques and Braak stages of NFTs) and CDR-SOB categories, the existence of some outliers should be noted. For example, among the 119 individuals considered "normal" after an extensive clinical evaluation (CDR-SOB = 0), 47 (39.5%) had moderate or frequent neuritic plaques (ADNC outliers). On the other hand, of the 83 individuals with no or a few tangles or neuritic plaques, only 49 (59.0%) were considered clinically normal, and 25 (30.1%) had a CDR-SOB greater than or equal to 3.5, consistent with dementia (cognitive outliers).

The impact of increasing Braak stages of NFTs on the CDR-SOB outcome was evaluated using the subjects with Braak stage 0/I/II as the reference group and controlling for all the other demographic and neuropathologic variables. This full multivariable regression model confirmed the expected inverse association between Braak stage of NFTs and level of cognitive function because an isocortical stage of NFTs (Braak V/VI) predicted a higher CDR-SOB than stage 0/I/II across all categories of CDR-SOB. Compared with few NFTs (Braak 0 or an entorhinal stage of NFTs, Braak I/II), however, the limbic stage (Braak III/IV) was only associated with a higher risk of being CDR-SOB 0.5 to 3 (i.e. MCI) relative to being cognitively intact (CDR-SOB = 0) but did not predict a deeper cognitive impairment.

Similarly, the impact of increasing numbers of neuritic plaques on the CDR-SOB outcome was evaluated using the subjects with none or sparse neuritic plaques as the reference group and controlling for all the other demographic and neuropathologic variables. Compared with none/sparse neuritic plaques, moderate numbers of neuritic plaques by CERAD scoring predicted a higher CDR-SOB; this prediction was even stronger when frequent neuritic plaques were present.

Concurrent Pathologies—Some degree of vascular amyloid deposition was present in the brains of 66.6% (543 of 815) of subjects. Compared with not having any degree of CAA, the presence of mild CAA had no significant impact on CDR-SOB, whereas moderate and severe degrees of CAA were increasingly associated with worse cognition despite adjusting for CERAD plaque score besides all the other variables.

Although we excluded those individuals with a primary diagnosis of Parkinson disease or dementia with Lewy bodies, some concurrent "incidental" Lewy body pathology was present in 26.2% (218 of 832) of the study sample. As expected in any elderly cohort, a large proportion of subjects (≈80%) had some degree of small-vessel disease and/or atherosclerosis in the large vessels (i.e. circle of Willis, carotid arteries). Hippocampal sclerosis was present in only 6.6% (53 of 804) of the subjects. Interestingly, the presence of hippocampal sclerosis and a severe degree (but not lesser extent) of small-vessel disease were independently associated with worse cognition; by contrast, the presence of incidental Lewy bodies in any brain region did not have a statistically significant impact on dementia severity in this cohort.

Inverse Probability Weighting Model

Autopsy cohort studies may be subjected to selection biases related to the probability of death and to the decision of undergoing autopsy. However, controlling for potential autopsy-related selection bias by inverse probability weighting did not substantially change the direction or the magnitude of correlations (Table, Supplemental Digital Content 1, http://links.lww.com/NEN/A532).

DISCUSSION

The recent revisions of research criteria for AD at the earliest stages as well as the neuropathologic diagnostic criteria embody the idea that lesions appear in the brain well in advance of cognitive impairment and that the gradual accumulation of these lesions is associated with the progression from intact cognition through MCI and to dementia with increasing severity. To test the hypothesis that there is a pathologic continuum that parallels the clinical continuum of AD-associated cognitive impairment, we used the CDR-SOB scores (16) as clinical outcome, and the standard widely used descriptors of plaques and NFTs (19, 21) as main explanatory variables. The CDR-SOB scores reflect a continuous set of clinical diagnoses from normal, to MCI, and to severe dementia. Similarly, CERAD scores of neuritic plaques (21) and Braak stages of NFTs (19) are semi-quantitative measures that can be used to reflect the extent of the AD pathologic process (3, 4).

Demographic Data Predictive of Cognitive Impairment

Among the demographic data, the education level had a significant protective effect against cognitive impairment, confirming the beneficial effect of education on late-life cognition reported by others (27, 28). Two important findings should be noted. First, our full multivariable model demonstrated that the protective effect associated with education level was not mediated by an effect on the extent of pathologic changes, in agreement with a previous NACC study (29). Second, the use of the adjacent-categories logit model enabled us to reveal that education is protective not only with respect to a dementia diagnosis but also across the clinical continuum of cognitive aging, thus extending the finding of this previous study. Taken together, these observations suggest the existence of a cognitive (or brain) reserve that enables elderly people with a high education level to tolerate AD and/or vascular lesions without developing cognitive deficits. Moreover, the fairly strong risk reduction (ln[odds ratio] (OR) of −0.15 per 4-year unit of education) observed in this large cohort collected across multiple sites and geographic regions reinforces the importance of understanding the brain biology underlying this modifier of the clinical expression of AD neuropathologic changes (30, 31). Education level may well be a proxy variable for other factors, including socioeconomic status and related issues, but in any case, it is a readily measurable variable that has a major association with the cognitive change observed for a given amount of ADNC.

A younger age of death was associated with worse cognitive function close to death, even after controlling for the severity of AD and concomitant pathologies. This association was not a consequence of a shorter duration of disease from symptom onset in older individuals nor was it related to the *APOE* genotype (not shown). Although this observation may suggest a more aggressive rate of progression of clinical AD dementia in individuals with a younger age of onset, it may also reflect a bias in the characteristics of individuals referred to ADCs and, therefore, should be interpreted with caution (29, 32).

ADNCs Predictive of Cognitive Impairment

Previous quantitative postmortem studies have established that the amount and distribution of NFTs, but not the plaque burden, correlate with dementia severity or a surrogate of it such

as dementia duration (26, 32–43). Confirming these previous findings, our multivariable regression analysis yielded a strong negative association between Braak stage of NFTs and level of cognitive function, supporting the idea that the regional distribution of NFT accumulation is a continuum that maps well to clinical status. The observation that, unlike the isocortical stage (Braak V/VI), the limbic stage of NFTs (Braak III/IV) was only associated with a higher risk of MCI (i.e. CDR-SOB 0.5–3) but not moderate or severe deficits suggests that NFTs limited to the limbic system are more tightly linked to the onset of cognitive impairment, whereas the progression of cognitive impairment correlates better with the spreading of NFTs to the association cortex.

With this very large data set, we also observed a significant independent contribution of neuritic plaques to cognitive impairment, which is in agreement with another large population-based clinicopathologic study (44, 45). It should be noted that the CERAD scores reflect the amount of the subset of neuritic plaques rather than amyloid deposition per se (21). Compared with non-neuritic amyloid deposits, neuritic plaques induce a profound disruption of the surrounding neuropil (46, 47) and are typically associated with glial responses (reactive astrocytes and activated microglia) (48–51). Both periplaque neuropil changes and glial responses may progressively accumulate as the disease advances and contribute to cognitive impairment (39, 46, 50, 52). Moreover, dense-core (usually neuritic) plaques are a reservoir of oligomeric species of β-amyloid (Aβ) (53–56), which are associated with synaptic loss (54, 55), and have shown a closer correlation with cognitive impairment than Aβ deposits (57–59). Thus, the CERAD neuritic plaque scoring system may behave as a surrogate of all these Aβ-induced deleterious effects. The new guidelines for AD neuropathologic evaluation (3, 4) include both the CERAD neuritic plaque score and the modified Thal amyloid burden assessment (22), so further evaluation of the effects of neuritic plaques and amyloid deposits will be informed by future studies.

This large data set also provided us with an opportunity to describe the existence of a non-negligible proportion of outliers to the AD clinicopathologic continuum. The “ADNC outliers,” that is, 47 (39.5%) of 119 subjects with no cognitive impairment (CDR-SOB = 0) but substantial ADNC (singularly neuritic plaques), reinforce the idea that plaques can accumulate before the onset of clinical disease. The “cognitive outliers,” that is, 34 (41.0%) of 83 subjects with no or minimal ADNC but significant cognitive impairment (CDR-SOB ≥0), emphasize the importance of demographic variables and concurrent pathologies as modulators of cognitive function. Importantly, 46 (7.2%) of 640 individuals with a CDR-SOB greater than or equal to 3.5 (meeting criteria for at least mild dementia) and felt to have AD after extensive specialized evaluations had no or only sparse neuritic plaques, and 36 of these 46 individuals had mild to moderate dementia, the phase of disease that has been targeted in most therapeutic trials. These subjects represent 14% of the 251 people at this mild to moderate stage (CDR-SOB = 3.5–12.0) in this cohort, emphasizing the not-uncommon presence of phenocopies of clinical AD without “sufficient” ADNCs to explain cognitive failure, particularly in the setting of mild dementia. This result agrees with those of recent studies suggesting that 10% to 15% of subjects with a diagnosis of probable AD would have negative amyloid biomarkers (60, 61). A comparison between mildly to moderately demented subjects with none or sparse neuritic plaques and those with moderate or frequent neuritic plaques (Table 5) revealed that the former subgroup has also a lower Braak stage of NFTs, are less likely to carry the *APOE*ε4 allele, and are slightly less impaired, but their cognitive impairment cannot be explained by a lower education level or a higher burden of concurrent pathologies. This observation raises the question as to whether the cognitive impairment observed in these subjects could be explained by other more subtle pathologic processes, such as synaptic loss or neuritic changes that are not measured in current consensus neuropathologic protocols.

Concurrent Pathologies Contribute to Cognitive Impairment

Mixed pathologies, particularly incidental Lewy body pathology and cerebral infarcts, frequently coexist with plaques and NFTs in elderly individuals with dementia and have been suggested as features that account for cognitive impairment in community-dwelling elderly people (44, 62). We also evaluated the contribution of associated or concurrent pathologies with cognitive impairment. For example, compared with no CAA, moderate and severe CAA, but not mild CAA, had a negative impact on cognition after adjusting for all other demographic and neuropathologic variables. Previous studies also revealed an independent contribution of CAA to cognitive impairment (44, 45, 63, 64). Thus, CAA, particularly severe CAA, seems to contribute independently to cognitive dysfunction with a robust OR of more than 1.5. Whether this reflects an effect on vascular health or microhemorrhages, is a marker for overall elevated levels of amyloid deposition or reflects other underlying aspects of pathophysiology remains uncertain, but the strength of this association suggests an important role of CAA on cognitive dysfunction.

Although the presence of incidental Lewy bodies in the brain (in the brainstem, limbic system, or neocortex) was fairly frequent in this cohort (≈25%), the association with worse cognition was not statistically significant. However, it should be noted that our eligibility criteria precluded the inclusion of subjects with a primary clinical or pathologic diagnosis of Parkinson disease or dementia with Lewy bodies. Although the presence of diffuse Lewy bodies in the neocortex has been associated with dementia in patients with Parkinson disease (65, 66) and neocortical Lewy bodies are a key feature necessary for the pathologic diagnosis of dementia with Lewy bodies (67), the association of neocortical Lewy bodies with dementia in nonselected samples remains controversial (26, 44, 68–70).

The contribution of vascular ischemic burden and, in particular, small-vessel disease to cognitive impairment in AD patients has been described by a number of previous clinicopathologic studies (40, 44, 45, 68, 71–75). By contrast, hippocampal sclerosis has received comparatively much less attention despite its presumed ischemic origin in the elderly (76–78). More recently, hippocampal sclerosis has been linked to neurodegenerative diseases such as FTLD-like TDP43-positive pathology and, to a lesser extent, AD (79–82). In fact, pure hippocampal sclerosis (i.e. without any other concomitant pathology) only represents less than 3% in large autopsy series (83–85). Similarly to Lewy body pathology, subjects with a primary neuropathologic diagnosis of infarct, vascular dementia, FTLD, or pure hippocampal sclerosis were excluded from the present study, but our inclusion criteria allowed the presence of concurrent vascular lesions and hippocampal sclerosis as incidental or contributing pathologic diagnoses. After adjusting for all the other variables, both severe parenchymal small-vessel disease and the presence of hippocampal sclerosis predicted a worse cognitive status proximate to death. Of note, although atherosclerosis of the intracranial arteries has been associated with cognitive impairment independently of the AD pathologic burden and of the presence of brain infarcts (86), in this cohort, we found no impact of atherosclerosis of the large arteries on the CDR-SOB scores (not shown); this might reflect a relative bias against referral of patients with major strokes to ADCs for evaluation.

In summary, the results of our analyses demonstrate strong and independent contributions of both neuritic plaques and NFTs to cognitive impairment over the entire clinical course of AD (Fig. 2). They also emphasize the impact of education and concurrent vascular pathologies including CAA, small-vessel disease, and hippocampal sclerosis, on the antemortem level of cognitive performance, which may be more prominent in instances of intermediate levels of tangles and plaques. The data also reveal that a reasonably large number of individuals diagnosed with Alzheimer dementia at leading clinical centers after standardized and rigorous evaluations do not appear to have substantial numbers of ADNCs.

All the above factors likely contribute to the inexact nature of clinicopathologic correlations in AD, particularly with regard to subjects with mild dementia. Nonetheless, the data also show definitively that marked neuropathologic changes of advanced Braak stage V/VI and frequent neuritic plaques are nearly always (>97%) associated with a clinically observed dementia; 93% of the time, this was at least moderately severe (CDR-SOB ≥6.0). Why rare individuals (a few percent at most) escape cognitive impairments even in the face of observed severe neuropathologic changes remains uncertain, but recent data suggest that some individuals may be relatively resilient to the neurotoxic effects of tangles and plaques and have preserved neuronal number and synaptic elements (87). Understanding the factors that lead to resilience or susceptibility may provide new insights into the pathophysiology of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES

1. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement J Alzheimers Assoc. 2011; 7:270–79.
2. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement J Alzheimers Assoc. 2011; 7:263–69.
3. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement J Alzheimers Assoc. 2012; 8:1–13.
4. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: A practical approach. Acta Neuropathol (Berl). 2012; 123:1–11. [PubMed: 22101365]
5. Arriagada PV, Marzloff K, Hyman BT. Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. Neurology. 1992; 42:1681–88. [PubMed: 1307688]
6. Schmitt FA, Davis DG, Wekstein DR, et al. “Preclinical” AD revisited: Neuropathology of cognitively normal older adults. Neurology. 2000; 55:370–76. [PubMed: 10932270]
7. Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol. 2003; 62:1087–95. [PubMed: 14656067]
8. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006; 66:1837–44. [PubMed: 16801647]
9. Price JL, McKeel DW Jr, Buckles VD, et al. Neuropathology of nondemented aging: Presumptive evidence for preclinical Alzheimer disease. Neurobiol Aging. 2009; 30:1026–36. [PubMed: 19376612]
10. Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med. 2012; 367:795–804. [PubMed: 22784036]

11. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. Neurobiol Aging. 1997; 18:S1–2. [PubMed: 9330978]
12. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: A review of the literature. J Neuropathol Exp Neurol. 2012; 71:362–81. [PubMed: 22487856]
13. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): Clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Dis Assoc Disord. 2006; 20:210–16. [PubMed: 17132964]
14. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) database: The Uniform Data Set. Alzheimer Dis Assoc Disord. 2007; 21:249–58. [PubMed: 17804958]
15. Weintraub S, Salmon D, Mercaldo N, et al. The Alzheimer's Disease Centers' Uniform Data Set (UDS): The neuropsychologic test battery. Alzheimer Dis Assoc Disord. 2009; 23:91–101. [PubMed: 19474567]
16. Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology. 1993; 43:2412–14. [PubMed: 8232972]
17. O'Bryant SE, Waring SC, Cullum CM, et al. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: A Texas Alzheimer's research consortium study. Arch Neurol. 2008; 65:1091–95. [PubMed: 18695059]
18. O'Bryant SE, Lacritz LH, Hall J, et al. Validation of the new interpretive guidelines for the Clinical Dementia Rating Scale Sum of Boxes score in the National Alzheimer's Coordinating Center database. Arch Neurol. 2010; 67:746–49. [PubMed: 20558394]
19. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl). 1991; 82:239–59. [PubMed: 1759558]
20. Braak H, Alafuzoff I, Arzberger T, et al. Staging of Alzheimer disease–associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol (Berl). 2006; 112:389–404. [PubMed: 16906426]
21. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology. 1991; 41:479–86. [PubMed: 2011243]
22. Thal DR, Rüb U, Orantes M, et al. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology. 2002; 58:1791–800. [PubMed: 12084879]
23. Agresti, A.; Agresti, A. Categorical Data Analysis [Internet]. John Wiley & Sons, Inc.; Hoboken, NJ: 2002. Available at: http://doi.wiley.com/10.1002/0471249688 [Accessed May 30, 2013]
24. Yee TM. The VGAM package for categorical data analysis. J Stat Softw. 2010; 32:1–34.
25. Haneuse S, Schildcrout J, Crane P, et al. Adjustment for selection bias in observational studies with application to the analysis of autopsy data. Neuroepidemiology. 2009; 32:229–39. [PubMed: 19176974]
26. Haneuse S, Larson E, Walker R, et al. Neuropathology-based risk scoring for dementia diagnosis in the elderly. J Alzheimers Dis J. 2009; 17:875–85.
27. Katzman R. Education and the prevalence of dementia and Alzheimer's disease. Neurology. 1993; 43:13–20. [PubMed: 8423876]
28. EClipSE Collaborative Members. Brayne C, Ince PG, Keage HAD, McKeith IG, Matthews FE, et al. Education, the brain and dementia: neuroprotection or compensation? Brain J Neurol. 2010; 133:2210–6.
29. Roe CM, Xiong C, Miller JP, et al. Education and Alzheimer disease without dementia: Support for the cognitive reserve hypothesis. Neurology. 2007; 68(3):223–28. [PubMed: 17224578]
30. Bennett DA, Wilson RS, Schneider JA, et al. Education modifies the relation of AD pathology to level of cognitive function in older persons. Neurology. 2003; 60:1909–15. [PubMed: 12821732]
31. Bennett DA, Schneider JA, Wilson RS, et al. Education modifies the association of amyloid but not tangles with cognitive function. Neurology. 2005; 65:953–55. [PubMed: 16186546]

32. Monsell SE, Mock C, Roe CM, et al. Comparison of symptomatic and asymptomatic persons with Alzheimer disease neuropathology. Neurology. 2013; 80:2121–29. [PubMed: 23645594]
33. Arriagada PV, Growdon JH, Hedley-Whyte ET, et al. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology. 1992; 42:631–39. [PubMed: 1549228]
34. Hyman BT, Marzloff K, Arriagada PV, et al. The lack of accumulation of senile plaques or amyloid burden in Alzheimer's disease suggests a dynamic balance between amyloid deposition and resolution. J Neuropathol Exp Neurol. 1993; 52:594–600. [PubMed: 8229078]
35. Bierer LM, Hof PR, Purohit DP, et al. Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. Arch Neurol. 1995; 52:81–88. [PubMed: 7826280]
36. Gómez-Isla T, Hollister R, West H, et al. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. Ann Neurol. 1997; 41:17–24. [PubMed: 9005861]
37. Giannakopoulos P, Herrmann FR, Bussière T, et al. Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. Neurology. 2003; 60:1495–500. [PubMed: 12743238]
38. Ingelsson M, Fukumoto H, Newell KL, et al. Early Abeta accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain. Neurology. 2004; 62:925–31. [PubMed: 15037694]
39. Serrano-Pozo A, Mielke ML, Gómez-Isla T, et al. Reactive glia not only associates with plaques but also parallels tangles in Alzheimer's disease. Am J Pathol. 2011; 179:1373–84. [PubMed: 21777559]
40. Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer disease: The Nun Study. JAMA. 1997; 277:813–17. [PubMed: 9052711]
41. Grober E, Dickson D, Sliwinski MJ, et al. Memory and mental status correlates of modified Braak staging. Neurobiol Aging. 1999; 20:573–79. [PubMed: 10674422]
42. Gold G, Kövari E, Corte G, et al. Clinical validity of A beta-protein deposition staging in brain aging and Alzheimer disease. J Neuropathol Exp Neurol. 2001; 60:946–52. [PubMed: 11589425]
43. Bennett DA, Schneider JA, Wilson RS, et al. Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. Arch Neurol. 2004; 61:378–84. [PubMed: 15023815]
44. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet. 2001; 357:169–75. [PubMed: 11213093]
45. Matthews FE, Brayne C, Lowe J, et al. Epidemiological pathology of dementia: Attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. Plos Med. 2009; 6:e1000180. [PubMed: 19901977]
46. Knowles RB, Gomez-Isla T, Hyman BT. Abeta associated neuropil changes: Correlation with neuronal loss and dementia. J Neuropathol Exp Neurol. 1998; 57:1122–30. [PubMed: 9862634]
47. Knowles RB, Wyart C, Buldyrev SV, et al. Plaque-induced neurite abnormalities: Implications for disruption of neural networks in Alzheimer's disease. Proc Natl Acad Sci U S A. 1999; 96:5274–79. [PubMed: 10220456]
48. Itagaki S, McGeer PL, Akiyama H, et al. Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. J Neuroimmunol. 1989; 24:173–82. [PubMed: 2808689]
49. Pike CJ, Cummings BJ, Cotman CW. Early association of reactive astrocytes with senile plaques in Alzheimer's disease. Exp Neurol. 1995; 132:172–79. [PubMed: 7789457]
50. Vehmas AK, Kawas CH, Stewart WF, et al. Immune reactive cells in senile plaques and cognitive decline in Alzheimer's disease. Neurobiol Aging. 2003; 24:321–31. [PubMed: 12498966]
51. Serrano-Pozo A, Muzikansky A, Gómez-Isla T, et al. Differential relationships of reactive astrocytes and microglia to fibrillar amyloid deposits in Alzheimer disease. J Neuropathol Exp Neurol. 2013; 72:462–71. [PubMed: 23656989]
52. Kashon ML, Ross GW, O'Callaghan JP, et al. Associations of cortical astrogliosis with cognitive performance and dementia status. J Alzheimers Dis Jad. 2004; 6:595–604.

53. Shankar GM, Li S, Mehta TH, et al. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med. 2008; 14:837–42. [PubMed: 18568035]
54. Koffie RM, Meyer-Luehmann M, Hashimoto T, et al. Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. Proc Natl Acad Sci U S A. 2009; 106:4012–17. [PubMed: 19228947]
55. Koffie RM, Hashimoto T, Tai H-C, et al. Apolipoprotein E4 effects in Alzheimer's disease are mediated by synaptotoxic oligomeric amyloid-β. Brain J Neurol. 2012; 135:2155–68.
56. Hong S, Quintero-Monzon O, Ostaszewski BL, et al. Dynamic analysis of amyloid β-protein in behaving mice reveals opposing changes in ISF versus parenchymal Aβ during age-related plaque formation. J Neurosci Off J Soc Neurosci. 2011; 31:15861–69.
57. McLean CA, Cherny RA, Fraser FW, et al. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann Neurol. 1999; 46:860–66. [PubMed: 10589538]
58. Lue LF, Kuo YM, Roher AE, et al. Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. Am J Pathol. 1999; 155:853–62. [PubMed: 10487842]
59. Näslund J, Haroutunian V, Mohs R, et al. Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline. JAMA. 2000; 283:1571–77. [PubMed: 10735393]
60. Johnson KA, Sperling RA, Gidicsin CM, et al. Florbetapir (F18-AV-45) PET to assess amyloid burden in Alzheimer's disease dementia, mild cognitive impairment, and normal aging. Alzheimers Dement J Alzheimers Assoc. 2013 pii: S1552-5260(12)02517-4.
61. Lowe VJ, Peller PJ, Weigand SD, et al. Application of the National Institute on Aging-Alzheimer's Association AD criteria to ADNI. Neurology. 2013; 80:2130–37. [PubMed: 23645596]
62. Schneider JA, Arvanitakis Z, Bang W, et al. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology. 2007; 69:2197–204. [PubMed: 17568013]
63. Pfeifer LA, White LR, Ross GW, et al. Cerebral amyloid angiopathy and cognitive function: The HAAS autopsy study. Neurology. 2002; 58:1629–34. [PubMed: 12058090]
64. Arvanitakis Z, Leurgans SE, Wang Z, et al. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. Ann Neurol. 2011; 69:320–27. [PubMed: 21387377]
65. Hurtig HI, Trojanowski JQ, Galvin J, et al. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology. 2000; 54:1916–21. [PubMed: 10822429]
66. Braak H, Rüb U, Jansen Steur ENH, et al. Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology. 2005; 64:1404–10. [PubMed: 15851731]
67. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB Consortium. Neurology. 2005; 65:1863–72. [PubMed: 16237129]
68. Sonnen JA, Larson EB, Crane PK, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol. 2007; 62:406–13. [PubMed: 17879383]
69. Zaccai J, Brayne C, McKeith I. Patterns and stages of alpha-synucleinopathy: Relevance in a population-based cohort. Neurology. 2008; 70:1042–48. [PubMed: 18362284]
70. Parkkinen L, Kauppinen T, PirttilÄ T, et al. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. Ann Neurol. 2005; 57:82–91. [PubMed: 15562510]
71. Nagy Z, Esiri MM, Jobst KA, et al. The effects of additional pathology on the cognitive deficit in Alzheimer disease. J Neuropathol Exp Neurol. 1997; 56:165–70. [PubMed: 9034370]
72. Heyman A, Fillenbaum GG, Welsh-Bohmer KA, et al. Cerebral infarcts in patients with autopsy-proven Alzheimer's disease: CERAD, part XVIII. Consortium to Establish a Registry for Alzheimer's Disease. Neurology. 1998; 51:159–62. [PubMed: 9674796]
73. White L, Petrovitch H, Hardman J, et al. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. Ann N Y Acad Sci. 2002; 977:9–23. [PubMed: 12480729]
74. Petrovitch H, Ross GW, Steinhorn SC, et al. AD lesions and infarcts in demented and non-demented Japanese-American men. Ann Neurol. 2005; 57:98–103. [PubMed: 15562458]
75. Troncoso JC, Zonderman AB, Resnick SM, et al. Effect of infarcts on dementia in the Baltimore Longitudinal Study of Aging. Ann Neurol. 2008; 64:168–76. [PubMed: 18496870]

76. Dickson DW, Davies P, Bevona C, et al. Hippocampal sclerosis: A common pathological feature of dementia in very old (> or = 80 years of age) humans. Acta Neuropathol (Berl). 1994; 88:212–21. [PubMed: 7810292]
77. Corey-Bloom J, Sabbagh MN, Bondi MW, et al. Hippocampal sclerosis contributes to dementia in the elderly. Neurology. 1997; 48:154–60. [PubMed: 9008511]
78. Kril JJ, Patel S, Harding AJ, et al. Patients with vascular dementia due to microvascular pathology have significant hippocampal neuronal loss. J Neurol Neurosurg Psychiatry. 2002; 72:747–51. [PubMed: 12023418]
79. Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord. 2002; 16:203–12. [PubMed: 12468894]
80. Amador-Ortiz C, Lin W-L, Ahmed Z, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann Neurol. 2007; 61:435–45. [PubMed: 17469117]
81. Nelson PT, Schmitt FA, Lin Y, et al. Hippocampal sclerosis in advanced age: Clinical and pathological features. Brain J Neurol. 2011; 134:1506–18.
82. Pao WC, Dickson DW, Crook JE, et al. Hippocampal sclerosis in the elderly: Genetic and pathologic findings, some mimicking Alzheimer disease clinically. Alzheimer Dis Assoc Disord. 2011; 25:364–68. [PubMed: 21346515]
83. Ala TA, Beh GO, Frey WH 2nd. Pure hippocampal sclerosis: A rare cause of dementia mimicking Alzheimer's disease. Neurology. 2000; 54:843–48. [PubMed: 10690974]
84. Jellinger K. Pure hippocampal sclerosis: A rare cause of dementia mimicking Alzheimer's disease. Neurology. 2000; 55:739–40. [PubMed: 10980757]
85. Leverenz JB, Agustin CM, Tsuang D, et al. Clinical and neuropathological characteristics of hippocampal sclerosis: A community-based study. Arch Neurol. 2002; 59:1099–106. [PubMed: 12117357]
86. Dolan H, Crain B, Troncoso J, et al. Atherosclerosis, dementia, and Alzheimer disease in the Baltimore Longitudinal Study of Aging cohort. Ann Neurol. 2010; 68:231–40. [PubMed: 20695015]
87. Perez-Nievas BG, Stein TD, Tai H-C, et al. Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. Brain J Neurol. 2013; 136:2510–26.

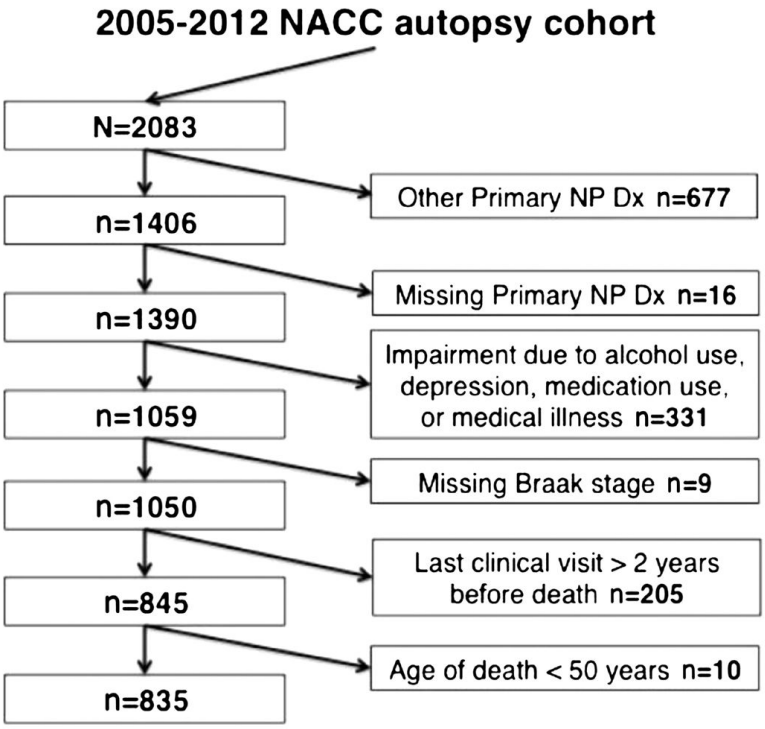

FIGURE 1.

Flowchart showing the selection procedure of study subjects. Of the 2,083 subjects from the 2005 to 2012 National Alzheimer Coordinating Center (NACC) autopsy cohort, 835 met all inclusion criteria and none of the exclusion criteria. Other primary neuropathologic diagnoses refer to conditions different from Alzheimer disease and included frontotemporal lobar degeneration, dementia with Lewy bodies, hippocampal sclerosis, vascular dementia, prion disease, Parkinson disease, Huntington disease, hypoxia, ischemia, necrosis, hemorrhage, and other non-neurodegenerative diagnosis. NP Dx, neuropathologic diagnosis.

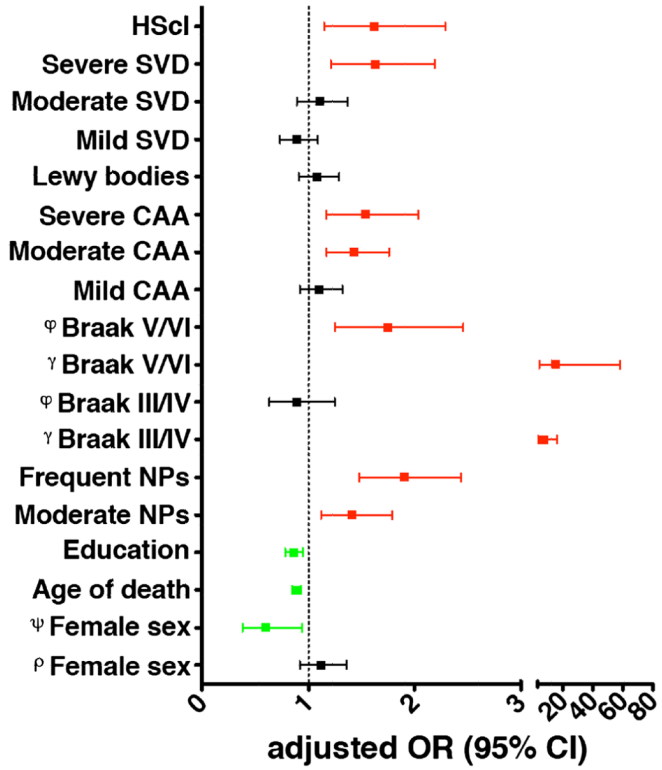

FIGURE 2.

Summary of the main results of this study (full model). Forest plot represents odds ratio ([OR] symbols) and 95% confidence interval ([CI] bars) of the association between each predictive variable and the outcome variable Clinical Dementia Rating scale–Sum of Boxes (CDR-SOB). Nonstatistically significant associations are depicted in black, statistically significant negative (protective) associations in green, and statistically significant positive (risk) associations in red. Two ORs (95% CI) are shown for female sex, one for the comparisons between the adjacent CDR-SOB categories 0, 0.5 to 3, 3.5 to 6, 6.5 to 12, and 12.5 to 17 (ρ) and the other for the comparison between the adjacent CDR-SOB categories 12.5 to 17 and 18 (ψ). Two ORs (95% CI) are shown for Braak NFT stages III/IV and V/VI, one for the adjacent CDR-SOB categories 0 and 0.5 to 3 (γ) and the other for the adjacent CDR-SOB categories 3.5 to 6, 6.5 to 12, 12.5 to 17, and 18 (φ). CAA, cerebral amyloid angiopathy; HScl, hippocampal sclerosis; NFT, neurofibrillary tangles; NPs, neuritic plaques; SVD, small-vessel disease (arteriosclerosis).

TABLE 1

Description of Demographic Characteristics of the Study Cohort by Clinical Disease Rating Scale–Sum of Boxes Intervals

	CDR-SOB 0.0	CDR-SOB 0.5–3.0	CDR-SOB 3.5–6.0	CDR-SOB 6.5–12.0	CDR-SOB 12.5–17.0	CDR-SOB 18.0	Row Total (% total)
No. subjects (row %)	119 (14.3)	76 (9.1)	80 (9.6)	171 (20.5)	152 (18.2)	237 (28.4)	835 (100.0)
Sex, n (row %)							
Male	55 (11.9)	43 (9.3)	49 (10.6)	103 (22.2)	95 (20.5)	118 (25.5)	463 (55.4)
Female	64 (17.2)	33 (8.9)	31 (8.3)	68 (18.3)	57 (15.3)	119 (32.0)	372 (44.6)
Age of death, years							
Mean	87.2	88.6	83.5	82.4	79.7	79.6	82.5
Median	88.0	89.5	84.0	83.0	81.0	80.0	84.0
Range	59.0–103.0	72.0–103.0	59.0–102.0	52.0–111.0	55.0–101.0	52.0–105.0	52.0–111.0
Education, years							
Mean	15.7	15.5	15.7	15.0	14.8	14.4	15.0
Median	16.0	16.0	16.0	16.0	15.0	16.0	16.0
Range	6.0–22.0	8.0–22.0	7.0–22.0	5.0–22.0	7.0–24.0	3.0–22.0	3.0–24.0
Missing data, n (row %)	1 (10.0)	1 (10.0)	1 (10.0)	3 (30.0)	1 (10.0)	3 (30.0)	10 (1.2)
Time from evaluation to death, days							
Mean	295.3	310.3	338.4	319.3	273.8	238.0	285.5
Median	274.0	284.0	310.5	305.0	241.5	202.0	251.0
Range	5.0–687.0	16.0–721.0	48.0–727.0	4.0–710.0	0.0–721.0	0.0–718.0	0.0–727.0
APOE genotype, n (row %)							
∈2/∈2	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
∈2/∈3	20 (38.5)	10 (19.2)	6 (11.5)	10 (19.2)	2 (3.8)	4 (7.7)	52 (6.2)
∈2/∈4	1 (5.0)	4 (20.0)	5 (25.0)	5 (25.0)	0 (0.0)	5 (25.0)	20 (2.4)
∈3/∈3	78 (24.6)	34 (10.7)	24 (7.6)	59 (18.6)	51 (16.1)	71 (22.4)	317 (38.0)
∈3/∈4	13 (5.0)	14 (5.4)	23 (8.8)	65 (24.9)	55 (21.1)	91 (34.9)	261 (31.3)
∈4/∈4	0 (0.0)	3 (4.5)	3 (4.5)	11 (16.7)	20 (30.3)	29 (43.9)	66 (7.9)
Missing data, n (row %)	7 (5.9)	10 (8.5)	19 (16.1)	21 (17.8)	24 (20.3)	37 (31.4)	118 (14.1)

APOE, apolipoprotein E.

TABLE 2

Alzheimer Disease Neuritic Plaque and Neurofibrillary Tangle Categories by Clinical Disease Rating Scale–Sum of Boxes Intervals

Braak Stage	Neuritic Plaques	Clinical Disease Rating Scale–Sum of Boxes Score						Row Total
		0.0	0.5–3.0	3.5–6.0	6.5–12.0	12.5–17.0	18.0	
None/I/II	None/sparse	49 (59.0)	9 (10.8)	8 (9.6)	13 (15.7)	3 (3.6)	1 (1.2)	83
		(44.6–72.0)	(4.7–23.0)	(4.0–21.5)	(7.9–28.8)	(0.9–13.5)	(0.1–9.8)	
	Moderate	17 (54.8)	6 (19.3)	2 (6.5)	4 (12.9)	0 (0.0)	2 (6.5)	31
		(32.6–75.3)	(7.1–42.8)	(1.2–27.6)	(3.8–35.6)	(0.0–18.3)	(1.2–27.6)	
	Frequent	6 (54.6)	1 (9.1)	1 (9.1)	1 (9.1)	0 (0.0)	2 (18.2)	11
		(21.7–83.8)	(1.0–48.9)	(1.0–48.9)	(1.0–48.9)	(0.0–38.8)	(3.5–57.5)	
III/IV	None/sparse	22 (40.0)	18 (32.7)	8 (14.6)	4 (7.3)	3 (5.5)	0 (0.0)	55
		(24.7–57.6)	(18.9–50.5)	(6.1–31.0)	(2.1–22.0)	(1.4–19.6)	(0.0–11.2)	
	Moderate	11 (13.3)	19 (22.9)	15 (18.1)	23 (27.7)	6 (7.2)	9 (10.8)	83
		(6.2–26.0)	(13.1–36.9)	(9.6–31.5)	(16.9–42.0)	(2.6–18.5)	(4.7–23.0)	
	Frequent	9 (13.4)	7 (10.5)	15 (22.4)	17 (25.4)	11 (16.4)	8 (11.9)	67
		(5.9–27.9)	(4.1–24.3)	(11.9–38.0)	(14.1–41.2)	(7.8–31.4)	(4.9–26.1)	
V/VI	None/sparse	1 (11.1)	2 (22.2)	0 (0.0)	3 (33.3)	3 (33.3)	0 (0.0)	9
		(1.3–54.9)	(4.3–64.3)	(0.0–43.6)	(8.6–72.6)	(8.6–72.6)	(0.0–43.6)	
	Moderate	1 (1.5)	7 (10.1)	6 (8.7)	14 (20.3)	24 (34.8)	17 (24.6)	69
		(0.2–11.6)	(4.0–23.6)	(3.1–21.8)	(10.5–35.5)	(21.7–50.7)	(13.7–40.2)	
	Frequent	3 (0.7)	7 (1.6)	25 (5.9)	92 (21.6)	102 (23.9)	198 (46.4)	427
		(0.2–2.8)	(0.6–4.2)	(3.5–9.6)	(16.8–27.2)	(18.9–29.7)	(40.1–52.7)	
Column total		119	76	80	171	152	237	835

Values represent the frequencies (row proportions) and (confidence intervals) of subjects with a given level of Alzheimer disease pathology within each Clinical Disease Rating Scale–Sum of Boxes interval.

TABLE 3

Description of Concurrent Pathologies by Clinical Disease Rating Scale–Sum of Boxes Intervals

	CDR-SOB 0.0	CDR-SOB 0.5–3.0	CDR-SOB 3.5–6.0	CDR-SOB 6.5–12.0	CDR-SOB 12.5–17.0	CDR-SOB 18.0	Row Total
Lewy bodies, n (row %)							
Brainstem	3 (12.0)	2 (8.0)	3 (12.0)	5 (20.0)	3 (12.0)	9 (36.0)	25
Limbic	5 (6.8)	4 (5.5)	6 (8.2)	16 (21.9)	16 (21.9)	26 (35.6)	73
Neocortical	2 (3.4)	1 (1.7)	4 (6.8)	17 (28.8)	11 (18.6)	24 (40.7)	59
Other	0 (0.0)	3 (4.9)	0 (0.0)	14 (22.9)	19 (31.1)	25 (41.0)	61
No Lewy bodies	108 (17.6)	65 (10.6)	67 (10.9)	119 (19.4)	102 (16.6)	153 (24.9)	614
Missing/not accessed	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	3
Hippocampal sclerosis, n (row %)							
Yes	0 (0.0)	1 (1.9)	7 (13.2)	6 (11.3)	12 (22.6)	27 (50.9)	53
No	109 (14.5)	66 (8.8)	71 (9.4)	160 (21.3)	138 (18.4)	207 (27.6)	751
Missing/not accessed	10 (32.3)	9 (29.0)	2 (6.4)	5 (16.1)	2 (6.4)	3 (9.7)	31
CAA, n (row %)							
None	70 (25.6)	39 (14.3)	34 (12.4)	52 (19.0)	35 (12.8)	43 (15.7)	273
Mild	32 (13.6)	21 (8.9)	24 (10.2)	61 (26.0)	38 (16.2)	59 (25.1)	235
Moderate	11 (5.8)	9 (4.7)	11 (5.8)	37 (19.5)	49 (25.8)	73 (38.4)	190
Severe	4 (3.4)	6 (5.1)	11 (9.3)	15 (12.7)	28 (23.7)	54 (45.8)	118
Missing/not accessed	2 (10.0)	1 (5.0)	0 (0.0)	6 (30.0)	3 (15.0)	8 (40.0)	20
Arteriosclerosis, n (row %)							
None	15 (11.6)	15 (11.6)	17 (13.2)	29 (22.5)	26 (20.1)	27 (20.9)	129
Mild	55 (19.9)	26 (9.4)	28 (10.1)	62 (22.5)	45 (16.3)	60 (21.7)	276
Moderate	21 (11.5)	20 (10.9)	17 (9.3)	40 (21.9)	29 (15.8)	57 (31.1)	183
Severe	4 (6.7)	4 (6.7)	7 (11.7)	8 (13.3)	6 (10.0)	31 (51.7)	60
Missing/not accessed	24 (12.8)	11 (5.9)	11 (5.9)	32 (17.1)	46 (24.6)	63 (33.7)	187
Atherosclerosis, n (row %)							
None	18 (11.5)	14 (8.9)	12 (7.6)	34 (21.7)	32 (20.4)	47 (29.9)	157
Mild	55 (17.0)	31 (9.6)	33 (10.2)	69 (21.3)	60 (18.5)	76 (23.5)	324
Moderate	36 (14.3)	22 (8.7)	26 (10.3)	48 (19.0)	43 (17.1)	77 (30.6)	252
Severe	10 (10.1)	7 (7.1)	8 (8.1)	20 (20.2)	17 (17.2)	37 (37.4)	99
Missing/not accessed	0 (0.0)	2 (66.6)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3

Values represent the frequencies (row proportions) of subjects with a given level of concurrent pathology within each Clinical Disease Rating Scale-Sum of Boxes interval. CAA, cerebral amyloid angiopathy.

TABLE 4

Summary of Results of the Adjacent-Categories Multivariable Regression Model

	Model 1 (Only Demographics)		Model 2 (Model 1 + Neuritic Plaques + NFTs)		Model 3 (Model 2 + Concurrent Pathologies)	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Sex (female as reference)						
at $k = 1, 2, 3, 4$	1.12 (0.99–1.26)	0.063	1.12 (0.96–1.30)	0.148	1.12 (0.92–1.36)	0.265
at $k = 5$	0.55 (0.38–0.79)	0.001	0.53 (0.36–0.76)	0.001	0.60 (0.38–0.94)	0.027
Age of death (in 5-year units)	0.89 (0.87–0.92)	<0.001	0.91 (0.88–0.94)	<0.001	0.89 (0.85–0.93)	<0.001
Education (in 4-year units)	0.90 (0.85–0.95)	<0.001	0.85 (0.79–0.92)	<0.001	0.86 (0.78–0.95)	0.002
Neuritic plaques (CERAD) (none/sparse as reference)						
Moderate			1.45 (1.21–1.74)	<0.001	1.41 (1.12–1.79)	0.004
Frequent			1.85 (1.51–2.25)	<0.001	1.90 (1.48–2.44)	<0.001
NFTs (Braak) (none/I/II as reference)						
Stage III/IV						
at $k = 1$			4.75 (2.55–8.85)	<0.001	7.56 (3.50–16.32)	<0.001
at $k = 2, 3, 4, 5$			1.06 (0.81–1.39)	0.660	0.89 (0.63–1.25)	0.494
Stage V/VI						
at $k = 1$			9.84 (3.41–28.36)	<0.001	15.39 (4.08–58.06)	<0.001
at $k = 2, 3, 4, 5$			2.15 (1.63–2.83)	<0.001	1.75 (1.25–2.46)	0.001
CAA (none as reference)						
Mild					1.10 (0.92–1.32)	0.283
Moderate					1.43 (1.17–1.76)	0.001
Severe					1.54 (1.17–2.04)	0.002
Lewy bodies (present vs absent)					1.08 (0.91–1.29)	0.363
Arteriosclerosis (none as reference)						
Mild					0.89 (0.73–1.09)	0.274
Moderate					1.11 (0.89–1.37)	0.351
Severe					1.63 (1.21–2.19)	0.001
Hippocampal sclerosis (present vs absent)					1.62 (1.15–2.29)	0.006

Six ordinal levels of the response variable CDR-SOB, that is, 0.0, 0.5 to 3.0, 3.5 to 6.0, 6.5 to 12.0, 12.5 to 17.0, and 18.0, are represented by $k = 0, 1, 2, 3, 4, 5$. Examples of interpretation based on Model 3: 1) (effect of education) Holding other factors constant, the odds ratio (OR) of having CDR-SOB at a certain category versus the adjacent lower category associated with every 4-year increase in education is 0.86, with a 95% confidence interval (95% CI) of 0.78 to 0.95. 2) (effect of CERAD) Holding other factors constant, the odds of having CDR-SOB at a certain category versus the adjacent lower category for subjects with moderate neuritic plaques are 1.41 times the odds for subjects with sparse or no neuritic plaques, with a 95% CI of 1.12 to 1.79. 3) Holding other factors constant, the odds of having CDR-SOB at a certain category versus the adjacent lower category for subjects with frequent neuritic plaques are 1.90 times the odds for subjects with sparse or no neuritic plaques, with a 95% CI of 1.48 to 2.44. Note that 2 ORs (95% CI) are shown for sex: the first corresponds to the comparisons between each of the CDR-SOB categories (0.5–3.0, 3.5–6.0, 6.5–12.0, 12.5–17.0) and its adjacent lower category ($k = 1, 2, 3, 4$); whereas the second refers to the comparison between the CDR-SOB adjacent categories (12.5–17.0 and 18.0; $k = 5$). Similarly, 2 ORs (95% CI) are shown for each Braak NFT stage: the first refers to the comparison between CDR-SOB (0.5–3.0) and CDR-SOB = 0 ($k = 1$), whereas the second refers to the comparisons between each of the CDR-SOB categories (3.5–6.0, 6.5–12.0, 12.5–17.0 and 18.0) and its adjacent lower category ($k = 2, 3, 4, 5$).

TABLE 5

Comparison of Eligible Subjects With Clinical Dementia Rating Scale–Sum of Boxes 3.5 to 12.0 (Mild to Moderate Dementia) With None/Sparse or Moderate/Frequent Neuritic Plaques

	None/Sparse Neuritic Plaques (n = 36)	Moderate/Frequent Neuritic Plaques (n = 215)	p
Demographic variables			
Sex, n female (%)	12 (33.3)	87 (40.5)	0.4654
Education, years	14.5 ± 3.7	15.3 ± 3.0	0.2371
Age of onset, years	77.1 ± 13.7	74.4 ± 9.2	0.3152
Age of death, years	84.6 ± 11.5	82.4 ± 8.9	0.2137
Disease duration, years	6.6 ± 3.7	7.7 ± 3.9	0.1805
Cognitive variables			
CDR-SOB	6.5 (5.0–10.0)*	9.0 (6.0–11.0)*	0.0482*
MMSE	21.8 ± 4.0*	18.3 ± 5.9*	0.0002*
Trail-Making Test, Part B, seconds	208 ± 91	239 ± 78	0.2752
APOE genotype			
*APOE*ε4 carriers, n (%)	10 (34.5)*	102 (56.0)*	0.0440*
*APOE*ε4 alleles, n (%)	10 (17.2)*	116 (31.9)*	0.0297*
Neuropathologic variables			
Braak V/VI, n (%)	3 (8.3)*	137 (63.7)*	<0.0001*
Braak III/IV, n (%)	12 (33.3)	70 (32.6)	
Braak 0/I/II, n (%)	21 (58.3)*	8 (3.7)*	
Moderate/severe CAA, n (%)	8 (22.2)	66 (13.8)	0.3272
Moderate/severe arteriosclerosis, n (%)	15 (45.4)	57 (33.1)	0.1665
Lacunar infarcts, n (%)	7 (19.4)	25 (11.7)	0.1883
Cortical microinfarcts, n (%)	10 (27.8)	39 (18.2)	0.1805
Moderate/severe atherosclerosis, n (%)	12 (33.3)	90 (42.1)	0.3637
Large infarcts, n (%)	4 (11.1)	12 (5.6)	0.2599
Cerebral hemorrhages, n (%)	2 (5.9)	9 (4.2)	0.6500
Hippocampal sclerosis, n (%)	4 (11.4)	9 (4.3)	0.0981
Lewy body pathology, n (%)	7 (19.4)	58 (27.0)	0.4144

The subjects with CDR-SOB 3.5 to 12.0 and none/sparse neuritic plaques may be enrolled in clinical trials with disease-modifying drugs in mild to moderate AD but represent “cognitive outliers” in the AD clinicopathologic continuum. In fact, they do not appear to have Alzheimer disease, as a lower Braak NFT stage and an under-representation of the *APOE*ε4 allele indicate. They are less impaired, but their cognitive impairment cannot be explained by a lower education level or a higher burden of concurrent vascular or Lewy body pathologies.

Data represent mean ± SD. Numbers in parenthesis indicate the proportion of subjects with the finding in each group. Percents may vary because of missing data. Proportions were compared with Fisher exact test. Continuous variables were compared with unpaired *t*-test with Welch correction. Mann-Whitney U test was used for CDR-SOB.

APOE, apolipoprotein E; CAA, cerebral amyloid angiopathy; CDR-SOB, Clinical Dementia Rating scale Sum Of Boxes; MMSE, Mini Mental State Examination.

*Statistically significant results ($p < 0.05$).