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Clinical Dementia Rating Performed Several Years prior to Death Predicts Regional Alzheimer's Neuropathology

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Abstract

Aims—To assess the relationships between early and late antemortem measures of dementia severity and Alzheimer disease (AD) neuropathology severity.

Methods—40 residents of a nursing home, average age at death 82.0, participated in this longitudinal cohort study with postmortem assessment. Severity of dementia was measured by Clinical Dementia Rating (CDR) at two time points, averaging 4.5 and 1.0 years before death. Densities of postmortem neuritic plaques (NPs) and neurofibrillary tangles (NFTs) were measured in the cerebral cortex, hippocampus, and entorhinal cortex.

Results—For most brain areas, both early and late CDRs were significantly associated with NPs and NFTs. CDRs assessed proximal to death predicted NFTs beyond the contribution of early CDRs. NPs were predicted by both early and late CDRs. NPs were predictive of both early and late CDRs after controlling for NFTs. NFTs were only associated significantly with late CDR in the cerebral cortex after controlling for NPs.

Conclusions—Even if assessed several years before death, dementia severity is associated with AD neuropathology. NPs are more strongly associated with dementia severity than NFTs. NFTs consistently associate better with late than early CDR, suggesting that these neuropathological changes may occur relatively later in the course of the disease.

Keywords

Dementia severity; Alzheimer's disease; Neuropathology; Neuritic plaques; Neurofibrillary tangles

Introduction

There has been considerable interest over the last decade in the relationship between progressive cognitive decline [4, 18, 23] and underlying neuropathology associated with Alzheimer's disease (AD), mainly neuritic plaques (NPs) and neurofibrillary tangles (NFTs) [2, 27]. The connection between dementia severity and neuropathology associated with AD is a key issue in defining the molecular mechanisms responsible for functional loss.

Dementia severity may be measured prospectively long before or near death, which occurs at different stages of the disease in different subjects, but in the absence of sensitive neuroimaging techniques the severity of AD neuropathology can be assessed only postmortem. However, most postmortem studies evaluate dementia severity at the time of death retrospectively [6], and in subjects who are mostly at severe stages of the disease [13, 20]. It is plausible that postmortem neuropathology might be more strongly associated with dementia severity near death than dementia severity long before death, simply because it is closer in time. Alternatively, if the postmortem neuropathology reflects changes that occurred long before death, it might be better related to dementia severity long before death. More interestingly, it is possible that different neuropathological features of AD, such as NPs and NFTs, are each associated with dementia severity at different stages of the disease. For example, it is possible that NFTs contribute to the early phases of disease [5, 15], whereas NPs to later stages and vice versa [1, 8, 9, 28] or the magnitude of these lesions may not be associated with cognitive dysfunction at all [3]. Studying the correlation of NP and NFT lesion density with measures of dementia severity proximal or distal to death could provide insight into these processes. Having prospective data on dementia severity of neuropathologically assessed subjects allows us to more directly ask when these neuropathological processes occur during the course of dementia progression.

The relationships of dementia severity with specific measures of neuropathology may reflect strong relationships among the different neuropathology measures themselves [6]. Thus, the relationships of dementia severity with these neuropathological measures would be clarified by evaluating the association with each, when the influence of the other measures is statistically removed from consideration [24]. The present study examined the associations, in various brain regions, of the density of postmortem NPs and NFTs with antemortem assessments of severity of dementia (using the Clinical Dementia Rating (CDR) Scale), both shortly before death and several years earlier. Having multiple CDR measures on the same subjects, we compared their relative associations with postmortem neuropathology. Similarly, we compared the specific contributions of NPs and NFTs to the associations of neuropathology with both early and late CDR.

Methods

Subjects

The subjects were 40 residents of an academic affiliate of the Mount Sinai School of Medicine, the Jewish Home and Hospital (JHH) in Manhattan and Bronx, N.Y., who were assessed for CDR at least twice during life and who came to autopsy upon death. The cohort included in the present analysis was ascertained as part of a larger clinical and epidemiologic study of early AD described in detail elsewhere [8, 9]. All assessment procedures were approved by the JHH and the Mount Sinai School of Medicine Institutional Review Boards. Autopsies were performed after receiving consent for autopsy from each subject's legal next of kin. As part of that study, all consenting residents and new admissions to the JHH were given mental status screening tests, and CDR [12, 14, 17] tests were administered to those residents who were either not demented or had mild cognitive impairment. These residents were then followed longitudinally and received CDR assessments at intervals that averaged 18 months until death. The autopsied brains were evaluated by an extensive neuropathological assessment protocol that has been described in detail [8, 9]. All quantitative neuropathological evaluations were made prior to the selection of subjects for this study and all neuropathological variables were assessed without knowledge of the subject's cognitive status. All subjects assessed for CDR at least two times prior to death, who met CERAD neuropathological criteria [16] for normal brain, definite, probable or possible AD (CERAD categories 1–4) without significant other neuropathologic lesions, and who had complete data were included in the study.

CDR Procedure

A multistep approach was applied to the assignment of CDR scores [14]. Initially, a CDR score was obtained following interviews of the subject and caregiver individually. A careful review of all information contained within each patient's medical chart was then performed by a second reviewer experienced in neuropsychological assessment of living elderly patients. These reviews included admitting diagnoses, nurse's notes, social work records, psychiatric and neurological consultation results, medications histories, results of mental status testing, and all other medical records and laboratory studies. All CDR scores and all pertinent chart information were then presented to a senior clinician (H.Z.G.) and a consensus CDR score was derived.

Neuropathological Assessment

The neuropathological assessment consisted of examining representative blocks from superior and midfrontal gyrus, orbital cortex, basal ganglia with basal forebrain, amygdala, hippocampus (rostral and caudal levels with adjacent parahippocampal and inferior temporal cortex), superior temporal gyrus, parietal cortex (angular gyrus), calcarine cortex, hypothalamus with mammillary bodies, thalamus, midbrain, pons, medulla, cerebellar vermis, and lateral cerebellar hemisphere. Sections from paraffin-embedded blocks were stained using hematoxylin and eosin, modified Bielschowsky, modified thioflavin S, anti- β -amyloid and anti- τ as described previously [8, 9]. Any case showing evidence of Lewy body formation in the substantia nigra or locus ceruleus underwent antiubiquitin staining of representative cerebral cortical sections for the identification of cortical Lewy bodies. Cases with Lewy body pathology or any other neuropathology not characteristic of AD were eliminated from the primary analyses described. Every case was evaluated for the extent of neuropathologic lesions using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic battery [16]. Multiple high-power fields (usually 5) were examined in each slide and the density of NFTs and NPs with and without cores were rated on a 4-point scale of absent, sparse, moderate, or severe according to the CERAD scoring criteria. For the statistical analyses, these ordinal scale estimates of NP and NFT density were treated as equally spaced. Additionally, quantitative data regarding the density of NPs in the mid-frontal gyrus (Brodmann area 9), orbital frontal cortex (Brodmann area 45/47), superior temporal gyrus (Brodmann area 21/22), inferior parietal cortex (Brodmann area 39) and calcarine cortex (Brodmann area 17) were also collected. For these quantitative measures of plaque density, 5 representative high-power fields (0.5 mm^2) were examined in each cortical region and an average density score was calculated for each region, expressed as mean plaque density per mm^2 . Only NPs (with and without cores) were included in the NP counts reported here. When plaques were unevenly distributed in any slide, plaques in the region of the slide with the highest density were counted.

Statistical Analyses

For subjects whose CDR was measured more than twice, only the first and last measurements were included in these analyses. Analyses of the relationship of NPs and NFTs to CDR were based on summary variables calculated from ratings of NP and NFT densities and on means of direct NP counts in the cortex. The following summary variables were derived from NFT density ratings: (1) sum of all ratings from all brain regions examined; (2) sum of all ratings in the 5 cerebral cortical regions studied; (3) NFT density ratings in the hippocampus, and (4) NFT density ratings in the entorhinal cortex. Similar summary variables were calculated for NPs, except that the summary variables for NP densities in the cerebral cortex were based on the sum of the average NP counts in each of the 5 cortical regions studied.

Partial correlations were used to assess the associations of the two CDR measurements with NPs and with NFTs in the whole brain, cerebral cortex, hippocampus and entorhinal cortex, controlling for age at death, and intervals between each of the two CDR measurements and death. Additional partial correlations were calculated to evaluate the supplemental usefulness of the respective CDRs beyond the usefulness of the other (i.e., the association of late CDR with neuropathology controlling for early CDR, and the association of early CDR with neuropathology controlling for late CDR). For example, the partial correlation of late CDR controlling for early CDR removes spurious association due to the association of neuropathology with early CDR and the association of early CDR with late CDR.

To assess the relative contributions of NPs and NFTs, similar partial correlations for each brain region were calculated (all controlling for age at death, and intervals between each of the two CDR measurements and death): the associations of a CDR with NPs controlling for the respective NFTs and the associations of a CDR with NFTs controlling for the respective NPs. For each of these types of partial correlations (such as NPs controlling for NFTs in the whole brain), the significance of the difference between the partial correlations of early and late CDRs was evaluated, taking into account the common variable (such as whole brain NPs) in the two partial correlations [10].

Results

The demographic characteristics of the sample are presented in table 1. Subjects had a mean age of 82.0 (SD = 11.4) at death and 54% (n = 30) were female. The early CDR was administered, on the average, over 4 years before death (mean = 4.5 years), while the late CDR was administered, on the average, 1 year (mean = 1.0 years) before death. The majority of the early CDR scores were of mild to moderate dementia severity or less (CDR = 2 or below, median = 1); none of the subjects had very severe or profound dementia (CDR categories 4 and 5, respectively). In contrast, the majority of late CDR scores were rated with at least severe dementia (median = 3). Thus, during the approximately 3.5 years between the first and last CDR assessments, most of the subjects progressed in their dementia severity from relatively mild dementia to severe dementia.

For all brain areas examined (table 2), both early and late CDRs were significantly associated with NP density values (except for early CDR in the hippocampus that reached trend level only). Partial correlations, controlling for age at death and intervals between CDR measurements and death, were between 0.29 and 0.46; the significance was between $p = 0.07$ and $p = 0.004$ (see table 2). The correlations of early and late CDRs with NPs in the different brain regions did not differ significantly. Only in the hippocampus did the late CDR (the CDR most proximal to death and neuropathological assessment) significantly supplement the early CDR (partial $r = 0.35$, $t = 2.61$, d.f. = 49, $p = 0.012$).

In contrast to the consistent results for NPs, CDRs were not as generally associated with the extent of NFTs in different brain areas. NFTs were significantly predicted by CDR scores assessed proximal to the time of death within the hippocampus, cerebral cortex, and aggregate NFT density estimates for the entire brain, but distal to time of death only in the cerebral cortex (see table 2). In addition, associations for late CDRs were consistently, but not statistically significantly, stronger than for early CDRs. Partial correlations for the supplemental contribution of the late CDRs beyond the early CDRs approached significance (p value between 0.025 and 0.14), but none of the early CDRs supplemented the late CDRs substantially (see table 2).

Table 3 presents CDR and AD neuropathology partial correlations of NPs controlling for NFTs and NFTs controlling for NPs, all controlling for age at death and intervals from

CDRs to death. The associations of NPs controlling for NFTs were significant in the entorhinal cortex for both early and late CDR measures, for early CDR in the whole brain, and for late CDR in the hippocampus. In contrast, for NFTs controlling for NPs, only the association with late CDR in the cerebral cortex was significant.

Discussion

The primary aim of this study was to compare the associations of early and late antemortem measures of dementia severity (CDR) with the severity of AD-related neuropathologic lesions. A second aim of the study was to determine which, if any, of the hallmark neuropathologic lesions of AD were best correlated with dementia severity early versus late in the course of disease.

The results indicated that estimates of dementia severity, as measured by the CDR, were good predictors of the severity and extent of NPs, irrespective of whether dementia severity was assessed proximal to the time of death (1 year) or an average of 4.5 years prior to death. However, the density of NPs was predicted better by dementia severity during the early course of disease, whereas dementia severity was associated with NFTs more consistently nearer death than long before death. These findings are consistent with our earlier cross-sectional studies of NP [8] and NFT [9] neuropathology as a function of dementia severity and are in good agreement with results published since then [e.g. 11, 18, 22, 23, 25]. These studies found that the density of NPs in the neocortex increased significantly with increasing dementia severity and that even cases of very mild or questionable dementia could be distinguished from non-demented elderly cases based on neocortical NP density. The density of NFTs in the neocortex was also found to increase systematically with increasing dementia severity, although NFT density increases were more reflective of mild to moderate dementia than of the even earlier stages of dementia reflected in NP density changes. In those cross-sectional studies, the estimates of dementia severity were based, to a large extent, on CDR scores derived by postmortem retrospective chart review and caregiver interviews, rather than the prospective longitudinal assessment of CDR in the current study. Thus, those earlier studies estimated dementia severity during the 6 months immediately prior to death rather than early in the course of the disease. The present results imply that estimates of dementia severity made even several years prior to death can reflect the severity of neuropathology observed at the time of death. This conclusion is in close agreement with results of Morris et al. [19], who suggested that subjects progress in dementia severity at rates that are dependent on the level of dementia severity at the time of first assessment.

Surprisingly, the association of NFTs in the entorhinal cortex with CDR did not achieve statistical significance even for CDR proximal to death. At least two alternative explanations can account for these observations. Moderate densities of NFTs are present in the entorhinal cortices and hippocampi of most elderly individuals, including those without significant dementia even at the time of death [9, 23]. Since moderate density of NFTs are present in the entorhinal cortices of most elderly individuals, additional increases in the density of NFTs could make only a modest and difficult to measure contribution to dementia severity. According to this hypothesis, neither early nor late CDR should be significantly associated with entorhinal cortex NFTs. An alternative interpretation that also accounts for the observed results is that NFTs in the entorhinal cortex are lesions that occur very early in the course of AD, and that by the time subjects were first assessed for dementia severity or died, the contribution of entorhinal cortex NFTs to dementia severity was no longer measurable because of factors such as neuronal death [22] and maximal involvement of NFTs in surviving neurons [11]. According to this hypothesis, there should be an association of entorhinal cortex NFTs with early CDR, but not with late CDR. Since entorhinal cortex NFTs were not associated with CDR measured early or late in the course of disease, the

results of the analyses performed here favor the former hypothesis. It can be argued, however, that the CDR does not have adequate fidelity to reflect subtle cognitive deficits that may result from NFTs in the entorhinal cortex. This argument, like any other argument that attributes the lack of an effect to the insensitivity of the measurement instruments, cannot be addressed by the current study.

When comparing the associations of early and late CDRs with AD neuropathology, different patterns of association emerge depending on type of neuropathology (NP vs. NFT). For NPs, both early and late CDRs (except in the hippocampus) were equally predictive of postmortem NP density. This might reflect a superimposed association due to NPs increasing fastest long before death, which would make the associations of early CDRs at least as strong as the late ones. These results are in keeping with an earlier cross-sectional study that showed that NPs accumulate primarily during the early stages of dementia and stabilize later on [8]. The density of NFTs, on the other hand, appears to be more strongly associated with CDR measures late in the course of disease (significance levels from 0.025 to 0.14 for late vs. early CDR, respectively). This result is consistent with a model suggesting that NFT accumulation happens mainly in more advanced stages of the disease, and that the correlation found between NFTs [11] and early CDR was driven by the higher CDR scores of subjects who entered the study with relatively advanced dementia. This interpretation is also consistent with previously published data [9] showing that increases in NFT density are observed after reaching a relatively high level of dementia severity (i.e., CDR scores of 1, 2 and higher).

To clarify the relationships of dementia severity with NPs and NFTs, we evaluated the association of CDR with NPs or NFTs, when the influence of the other was removed statistically. There were no significant associations of NFTs with either early or late CDR, after controlling for NPs, in any brain region except the cerebral cortex for the late CDR. In contrast, for NPs, after controlling for NFTs, the associations were significant (p value ranged from 0.006 to 0.03) in entorhinal cortex for both early and late CDR, in whole brain for early CDR and in hippocampus for late CDR. These findings, when viewed in light of the results discussed earlier, suggest that NPs are generally more informative of dementia severity than NFTs. The non-significant relationships with NFTs after controlling for NPs are consistent with the finding that the deposition of NPs accelerates the formation of tangles [23]. This suggests that increases in the density of NFTs are, at least partially, dependent on the formation of NPs.

The conclusion reached above is supported by results from other studies. Cummings et al. [6] examined the relationship between seven neuropathological features of AD in the entorhinal cortex and three cognitive measures, including CDR. All neuropathological measures, with the exception of NFT number and Thioflavine Index, correlated significantly with all three scales of cognitive status. Moreover, in a stepwise multiple regression model using all neuropathological measures as well as age, only NP index, A β load and plaque number contributed significantly to the equation, with NP index contributing the greatest to the model.

It should be noted that degenerative and neuropathological processes other than NPs and NFTs, such as synaptic or dendritic loss [26], and neurotransmitter [21] and neuropeptide deficits [7], which were not assessed in this study, also play a role in determining cognitive status. Additionally, we have chosen to examine the areas recommended by the CERAD for the assessment of AD pathology. It can be reasonably argued that assessment of other brain regions might have yielded different results.

The main advantages of this study are its prospective longitudinal ante- and postmortem design. The sample size, compared to other AD neuropathology studies with careful exclusion of diagnostically ambiguous cases, is relatively large although still not sufficiently large to permit stratification by CDR level. Due to the fairly long time between first and last CDRs, there was a substantial difference in mean CDR scores at the two assessments, suggesting that they were indicative of changing dementia severity rather than reflections of a condition that had already reached a plateau by the time of measurement. A limitation of this study is a nursing home sample that includes mainly Caucasian subjects with relatively high socioeconomic levels who may not be representative of the general elderly population. Another limitation of this study is that with the exception of NPs in the cerebral cortex, semiquantitative ratings were used. To assess the effect of having only four levels of NP severity, the cerebral cortex counts were rescaled to the marginal distribution of entorhinal cortex ratings, which were similarly positively skewed. The partial correlations with early and late CDRs were essentially identical to the original analysis using a continuous variable (data not shown).

In summary, these results suggest that dementia severity is predictive of neuropathological lesion density and severity, even if assessed 4.5 years before death. Generally, NPs are more strongly associated with dementia severity than NFTs. For NPs, late CDR is better associated than early CDR only in the hippocampus, while for NFTs there is a consistent trend for late CDR to be better associated than early CDR, suggesting that these neuropathological changes may occur relatively late in the course of the disease.

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References

1. Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology*. 1992; 42:631–639. [PubMed: 1549228]
2. Ball MJ. Neuronal loss, neurofibrillary tangles and granulovacuolar degeneration in the hippocampus with ageing and dementia. A quantitative study. *Acta Neuropathol (Berl)*. 1977; 37:111–118. [PubMed: 848276]
3. Bancher C, Jellinger K, Lassmann H, Fischer P, Leblhuber F. Correlations between mental state and quantitative neuropathology in the Vienna Longitudinal Study on Dementia. *Eur Arch Psychiatry Clin Neurosci*. 1996; 246:137–146. [PubMed: 8739399]
4. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE. Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. *Arch Neurol*. 2004; 61:378–384. [PubMed: 15023815]
5. Braak H, Braak E. Evolution of neuronal changes in the course of Alzheimer's disease. *J Neural Transm Suppl*. 1998; 53:127–140. [PubMed: 9700651]
6. Cummings BJ, Pike CJ, Shankle R, Cotman CW. Beta-amyloid deposition and other measures of neuropathology predict cognitive status in Alzheimer's disease. *Neurobiol Aging*. 1996; 17:921–933. [PubMed: 9363804]
7. Davis KL, Mohs RC, Marin DB, Purohit DP, Perl DP, Lantz M, Austin G, Haroutunian V. Neuropeptide abnormalities in patients with early Alzheimer disease. *Arch Gen Psychiatry*. 1999; 56:981–987. [PubMed: 10565496]
8. Haroutunian V, Perl DP, Purohit DP, Marin D, Khan K, Lantz M, Davis KL, Mohs RC. Regional distribution of neuritic plaques in the nondemented elderly and subjects with very mild Alzheimer disease. *Arch Neurol*. 1998; 55:1185–1191. [PubMed: 9740112]

9. Haroutunian V, Purohit DP, Perl DP, Marin D, Khan K, Lantz M, Davis KL, Mohs RC. Neurofibrillary tangles in nondemented elderly subjects and mild Alzheimer disease. *Arch Neurol*. 1999; 56:713–718. [PubMed: 10369312]
10. Hendrickson GF, Collins JR. Note correcting the results in 'Olkin's new formula for the significance of r_{13} vs. r_{23} compared with Hotelling's method'. *Am Educ Res J*. 1970; 7:639–641.
11. Hof PR, Bussiere T, Gold G, Kovari E, Giannakopoulos P, Bouras C, Perl DP, Morrison JH. Stereologic evidence for persistence of viable neurons in layer II of the entorhinal cortex and the CA1 field in Alzheimer disease. *J Neuropathol Exp Neurol*. 2003; 62:55–67. [PubMed: 12528818]
12. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982; 140:566–572. [PubMed: 7104545]
13. Iraizoz I, Guijarro JL, Gonzalo LM, de LS. Neuropathological changes in the nucleus basalis correlate with clinical measures of dementia. *Acta Neuropathol (Berl)*. 1999; 98:186–196. [PubMed: 10442559]
14. Marin DB, Flynn S, Mare M, Lantz M, Hsu MA, Laurans M, Paredes M, Shreve T, Zaklad GR, Mohs RC. Reliability and validity of a chronic care facility adaptation of the Clinical Dementia Rating Scale. *Int J Geriatr Psychiatry*. 2001; 16:745–750. [PubMed: 11536340]
15. McKee AC, Kosik KS, Kowall NW. Neuritic pathology and dementia in Alzheimer's disease. *Ann Neurol*. 1991; 30:156–165. [PubMed: 1910274]
16. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van BG, Berg L. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology*. 1991; 41:479–486. [PubMed: 2011243]
17. Morris JC, Ernesto C, Schafer K, Coats M, Leon S, Sano M, Thal LJ, Woodbury P. Clinical dementia rating training and reliability in multicenter studies: the Alzheimer's Disease Cooperative Study experience. *Neurology*. 1997; 48:1508–1510. [PubMed: 9191756]
18. Morris JC, Price AL. Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *J Mol Neurosci*. 2001; 17:101–118. [PubMed: 11816784]
19. Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L. Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol*. 2001; 58:397–405. [PubMed: 11255443]
20. Mouton PR, Martin LJ, Calhoun ME, Dal FG, Price DL. Cognitive decline strongly correlates with cortical atrophy in Alzheimer's dementia. *Neurobiol Aging*. 1998; 19:371–377. [PubMed: 9880038]
21. Perry EK, Haroutunian V, Davis KL, Levy R, Lantos P, Eagger S, Honavar M, Dean A, Griffiths M, McKeith IG. Neocortical cholinergic activities differentiate Lewy body dementia from classical Alzheimer's disease. *Neuroreport*. 1994; 5:747–749. [PubMed: 8018843]
22. Price JL, Ko AI, Wade MJ, Tsou SK, McKeel DW, Morris JC. Neuron number in the entorhinal cortex and CA1 in preclinical Alzheimer disease. *Arch Neurol*. 2001; 58:1395–1402. [PubMed: 11559310]
23. Price JL, Morris JC. Tangles and plaques in nondemented aging and 'preclinical' Alzheimer's disease. *Ann Neurol*. 1999; 45:358–368. [PubMed: 10072051]
24. Silverman W, Bobinski M, Wisniewski HM. Disentangling a complex pattern of interrelationships among multiple measures of Alzheimer neuropathology and clinical status: comments on Cummings, Pike, Shankle, and Cotman. *Neurobiol Aging*. 1996; 17:933–935. [PubMed: 9363805]
25. Storandt M, Grant EA, Miller JP, Morris JC. Longitudinal course and neuropathologic outcomes in original vs. revised MCI and in pre-MCI. *Neurology*. 2006; 67:467–473. [PubMed: 16894109]
26. Terry RD. Cell death or synaptic loss in Alzheimer disease. *J Neuropathol Exp Neurol*. 2000; 59:1118–1119. [PubMed: 11138931]
27. Tomlinson BE. Plaques, tangles and Alzheimer's disease. *Psychol Med*. 1982; 12:449–459. [PubMed: 7134306]
28. Vehmas AK, Kawas CH, Stewart WF, Troncoso JC. Immune reactive cells in senile plaques and cognitive decline in Alzheimer's disease. *Neurobiol Aging*. 2003; 24:321–331. [PubMed: 12498966]

Table 1

Description of the sample

	Mean or sum	SD	Min	Max
Age at death	82.00	11.40	62.72	102.38
First CDR to death, days	1,632	887	222	3,641
Last CDR to death, days	362	398	33	1,966
Early CDR	1.68	1.21	0	3
Late CDR	2.99	1.54	0	5
NPs				
Whole brain, sum of ratings	76.22	64.78	0	219.20
Cortex, count	12.29	7.50	0	20
Hippocampus, rating	1.29	0.93	0	3
Entorhinal cortex, rating	1.78	0.96	0	3
NFTs				
Whole brain, sum of ratings	20.95	12.69	0	45
Cerebral cortex, rating	7.34	6.59	0	18
Hippocampus, rating	2.37	0.94	0	3
Entorhinal cortex, rating	2.46	0.71	0	3

Rating scores correspond to: 0 = none, 1 = sparse, 3 = moderate, 5 = frequent/severe.

Associations and supplemental associations of early and late CDR for predicting NPs and NFTs, controlling for age at death and intervals from CDRs to death

Table 2

	Neuritic plaques						Neurofibrillary tangles					
	predictor (partial)			supplement (partial)			predictor (partial)			supplement (partial)		
	r	t	d.f.	p	r	t	r	t	d.f.	p	r	t
Whole brain												
Early CDR	0.46	3.11	35	0.004	0.25	1.52	0.14	0.28	1.53	35	0.14	-0.03
Late CDR	0.42	2.80	35	0.008	0.15	0.90	0.38	0.37	2.42	35	0.02	1.80
Cerebral cortex												
Early CDR	0.40	2.31	35	0.027	0.13	0.74	0.46	0.36	2.29	35	0.028	0.02
Late CDR	0.39	2.54	35	0.016	0.20	1.23	0.23	0.50	3.42	35	0.002	2.34
Hippocampus												
Early CDR	0.29	1.83	35	0.07	-0.06	0.37	0.71	0.18	1.08	35	0.29	-0.1
Late CDR	0.46	3.12	35	0.004	0.38	2.41	0.021	0.34	2.13	35	0.04	1.88
Entorhinal cortex												
Early CDR	0.39	2.56	35	0.015	0.24	1.48	0.15	0.00	0.00	35	0.99	-0.18
Late CDR	0.32	2.06	35	0.047	0.07	0.40	0.69	0.17	1.03	35	0.31	1.50

Table 3

Partial correlations controlling for age at death and intervals from CDRs to death (d.f. = 34)

	NPs (controlling for NFTs)		NFTs (controlling for NPs)	
	r	p	r	p
Whole brain				
Early CDR	0.40	0.01	– 0.04	0.79
Late CDR	0.27	0.10	0.16	0.33
Cerebral cortex				
Early CDR	0.22	0.20	0.21	0.21
Late CDR	0.17	0.31	0.37	0.02
Hippocampus				
Early CDR	0.24	0.15	0.02	0.90
Late CDR	0.35	0.03	0.11	0.52
Entorhinal cortex				
Early CDR	0.44	0.006	– 0.22	0.19
Late CDR	0.35	0.01	0.03	0.88