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Preclinical AD Workgroup staging: pathological correlates and potential challenges

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Abstract

The National Institute on Aging Preclinical Alzheimer's disease Workgroup (PADW) has issued a preliminary report with recommendations for classifying preclinical Alzheimer's disease (pAD) according to 3 early disease stages. Here we examine the PADW recommendations in relation to neuropathological features in a large, consecutive series of cognitively intact elderly persons, autopsied within a year after cognitive testing (n = 126 cognitively intact patients with mean age 83.7 years at death). Subjects were grouped based on a hypothetical construct correlating pathological features with PADW stages. Many cognitively intact individuals were classifiable as pAD (53/126 or 43%), as expected based on epidemiological and biomarker studies. Of these, most (48%) were in "stage 3", which corresponds to amyloid pathology with early neurodegeneration. As with prior studies, our data indicate that the development of neocortical neurofibrillary tangles is the key pathological event that is not observed in pAD cases: Braak stages III or IV pathology are hence not truly a substrate for "intermediate likelihood" that cognitive impairment is due to Alzheimer's disease (AD). We also stress the importance of comorbid non-Alzheimer's disease brain pathologies (hippocampal sclerosis, neocortical alpha-synucleinopathy, cerebrovascular disease, and brains with hippocampal neurofibrillary tangles but no cortical amyloid plaques) that can contribute to the development of cognitive impairment, or which may serve as confounds in the application of the PADW recommendations. While the final

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Disclosure statement
The authors have nothing to disclose.

Appendix A. Supplementary data
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recommendations from the PADW working group have not yet been released, this preliminary analysis provides a perspective on those recommendations from a neuropathological point of view.

Keywords

Nondemented; Biomarkers; MRI; CSF; Preclinical; Neuropathology; Normal

1. Introduction

Preclinical Alzheimer's disease (pAD) refers to individuals without antemortem cognitive changes but with some degree of confirmed Alzheimer's disease (AD)-related pathology, amyloid plaques, and neurofibrillary tangles (NFTs) (Arriagada et al., 1992b; Bennett et al., 2006; Crystal et al., 1988; Davis et al., 1999; Haroutunian et al., 1998; Hulette et al., 1998; Katzman et al., 1988; Knopman et al., 2003; Morris and Price, 2001; Price et al., 2009; Schmitt et al., 2000; Tomlinson et al., 1968; Troncoso et al., 1996). However, precise pathological criteria for pAD have not been defined. Current neuropathological consensus guidelines for AD diagnosis refer exclusively to individuals with substantial cognitive impairment meeting criteria for dementia (1997), and so the applicability of such criteria to individuals who were cognitively intact prior to death and autopsy remains unclear. As pathological analyses provide only a cross sectional view, it is unknown whether all cognitively intact subjects with varying degrees of amyloid plaques and NFTs would eventually progress to full-blown clinical AD. If a subset of these individuals do not progress clinically, then the utility of the pAD construct may be called into question. It is also possible that early disease mechanisms may be amenable to targeting by future therapies.

Given the importance of characterizing pAD stages that may allow for the development of rational prevention strategies, the National Institutes of Health (NIH) and Alzheimer's Association recently sponsored a panel of 14 experts, comprising the Preclinical AD Workgroup (PADW), to help define pAD (Alzheimer's Association, 2010). These researchers and clinicians, with expertise in various areas related to pAD, provided some preliminary recommendations. A key PADW proposal was to conceive of pAD as a multistage process, with each stage being amenable to detection via particular biomarkers.

There are many neurological and systemic factors that underlie cognitive deterioration in aged individuals (Barker et al., 2002; Jellinger, 2006; Jellinger and Attems, 2010; Nelson et al., 2009b; Schneider et al., 2009a), so therapy-relevant biomarkers are surrogates for specific pathologies — not for cognitive deterioration. The search for accurate antemortem biomarkers that may prove to be surrogates for specific disease states is of prime importance and necessarily will require confirmation by autopsy. Currently, neuropathological evaluation remains the diagnostic gold standard for specific neurodegenerative disease states. Potential AD biomarkers include cerebrospinal fluid markers (amyloid, tau, phospho-tau, isoprostanes, and others) and imaging modalities such as volumetric magnetic resonance imaging (MRI), diffusion tensor imaging, functional MRI, FDG-positron emission tomography (PET), and amyloid ligand-PET; AD biomarker data have been shown to be reasonably well correlated with the neuropathologic features of AD and predictive of future cognitive decline (Beckett et al., 2010; Blennow, 2004; Braskie et al., 2010; Buerger et al., 2006; Chertkow and Black, 2007; Chong and Sahadevan, 2005; Davatzikos et al., 2010; de Leon et al., 2007; Dubois et al., 2007; Engelborghs et al., 2007; Fagan et al., 2007; Haense et al., 2009; Jack et al., 2009, 2010a; Jagust et al., 2010; Johnson et al., 1998; Kapaki et al., 2003; Li et al., 2008; Mintun et al., 2006; Misra et al., 2009; Mormino et al., 2009; Morris et al., 2009; Peskind et al., 2006; Pike et al., 2007; Risacher et al., 2009, 2010; Rowe et al.,

2007; Smith et al., 2007; Stomrud et al., 2007, 2010; Walhovd et al., 2010; Weiner et al., 2010).

Prior studies using AD biomarkers appear to support a theoretical model for the progression of AD across the spectrum from normal aging to full-blown AD (Hardy and Selkoe, 2002; Jack et al., 2010b). In this model, amyloid plaques are followed successively by the development of tau pathology, neuronal dysfunction and degeneration, structural brain changes, cognitive decline and eventually the loss of function in activities of daily living that mark the transition to dementia. The recommendations of the PADW are largely based on this model of progression allowing the formation of many testable hypotheses regarding the construct of pAD and its implications for preclinical diagnosis, treatment, and prevention strategies.

Although the staging scheme for pAD as put forth by the PADW relates primarily to antemortem biomarkers, it is important to conceive of them within a framework that includes neuropathological information. The University of Kentucky Alzheimer's Disease Center (UK-ADC) follows a large cohort of subjects who are cognitively normal on enrollment, agree to undergo extensive longitudinal annual clinical evaluations, and consent to brain autopsy at death (Schmitt et al., 2001). In the period between 1989 and 2010, 164 cognitively intact subjects have come to autopsy from this group. Detailed quantitative neuropathological and neuropsychological data proximal to death are presented in an effort to characterize the features of pAD according to the proposed PADW stages. The goal is to provide new data that may aid in consideration of pAD for clinicians, researchers, and neuropathologists.

2. Methods

2.1. Subjects

Research volunteers studied in this report were from the UK-ADC clinical cohort, representing consecutive autopsies between 1989 and April 10, 2010, in accordance with University of Kentucky Institutional Review Board (IRB) protocols (Fig. 1). Inclusion criteria are cognitive and neurological normality by enrollment examination, and willingness to undergo annual cognitive testing, physical and neurological examinations, and brain donation at death. Excluded at enrollment were individuals with a history of substance abuse, major head injury, major psychiatric illness, medical illnesses that are nonstable, impairing, or that have an effect on the central nervous system (CNS), chronic infectious diseases, stroke or transient ischemic attack (TIA), encephalitis, meningitis, or epilepsy. Annual standardized assessment includes extensive medical, cognitive, social, and functional evaluations as previously described (Schmitt et al., 2001).

Overall at this research center between 1989 and April, 2010, 612 individuals came to autopsy with varying degrees of cognitive function and clinical diagnoses. Subjects who had developed dementia prior to autopsy (n = 448) were excluded from consideration of pAD. Of those followed from baseline normalcy, 270 patients were autopsied out of 310 that died while being followed (Fig. 1). Those that were still neurologically normal from this group at the time of the last evaluation (n = 164) serve as the focus of the present study. Subjects with pathologically-confirmed Parkinson's disease (n = 4) were not included in this group. The mental status testing of UK-ADC subjects has been described previously (Schmitt et al., 2001). Since 2005, a standard test battery was required by the National Alzheimer's Coordinating Center for all National Institute of Aging (NIA)-funded Alzheimer's Disease Centers (Morris et al., 2006; Weintraub et al., 2009). Only scores from the last evaluation prior to autopsy were used in the present analysis. Participants included in the present study were categorized into 3 groups: "cognitively intact", "mild cognitive impairment MCI)", and

"early AD". "Cognitively intact" individuals had no clinical diagnosis of MCI, AD, or other dementia. Cognitively intact subjects for whom the delay between final cognitive testing and death was greater than 1 year were excluded (n = 37 individuals who were cognitively intact on last testing). One case was excluded because she was evaluated 20 days prior to death from cancer and was unable to complete the evaluation. Individuals with MCI had a clinical-pathological consensus conference diagnosis based on consensus criteria (Petersen et al., 2001; Winblad et al., 2004). For MCI, individuals who died prior to 2001 were diagnosed using retrospective chart-based evaluations as described in detail previously (Jicha et al., 2010). No person was newly diagnosed or categorized as MCI for the purposes of the present study. MCI cases were selected based solely on clinical criteria without respect to pathological features and were not subtyped. "Early AD" cases had antemortem diagnosis of probable AD, with a clinical-pathological consensus diagnosis, histopathologically confirmed AD (NIA-Reagan High-likelihood [1997], Consortium to Establish a Registry for Alzheimer's Disease [CERAD] definite), with Braak stage V neurofibrillary pathology, and were seen within 2 years of death. All cases from our center meeting these criteria for early AD were included in this group. Using the above criteria, a total of 126 subjects displaying intact antemortem cognitive profiles were identified for inclusion in this study (Table 1). Mean days from last evaluation to autopsy was below 250 days in all cognitively intact groups. Average age at death was 83.7 years. MCI (n = 24) and early AD (n = 14) subjects, as described above, undergoing consecutive autopsy were also included for comparative purposes.

2.2. Tissue sampling and processing

Methods for neuropathological evaluations have been described in detail previously (Davis et al., 1999; Jicha et al., 2010; Nelson et al., 2007). Briefly, at least 24 different sections were sampled, and, after fixation, sectioned and stained with hematoxylin and eosin and the modified Bielschowsky method. The Gallyas stain was used for sections of the medial temporal lobe (MTL). Sections of the cortex and ventromedial temporal lobe structures were stained with 10D-5 or anti-Aβ antibody (Novacaster, Newcastle, UK).

NFTs, diffuse β-amyloid plaques (DP; plaques without surrounding dystrophic neurites), and neuritic β-amyloid plaques (NP; β-amyloid plaques surrounded or invested by argyrophilic dystrophic neurites) were counted as described previously (Nelson et al., 2007). An arithmetic mean was calculated from the count of the 5 most involved fields for DPs (number of DPs per 2.35 mm^2; 100× fields), NPs (number of NPs per 2.35 mm^2; 100× fields), and NFTs (number of NFTs per 0.586 mm^2; 400× fields) for each region using silver-stained sections of middle frontal gyrus, middle temporal gyrus, inferior parietal lobule, and occipital lobe including primary visual area. Mean neocortical counts represent an average derived from the 4 cortical areas described above. Medial temporal lobe (MTL) plaque and tangle counts represent an average derived from the entorhinal cortex, CA1, subiculum, and amygdala. Amyloid plaque results were cross correlated with results of anti-Aβ immunostains described above. Braak staging (Braak and Braak, 1991a) and CERAD plaque scores (Gearing et al., 1995) were used to determine NIA-Reagan diagnosis of pathological AD (1997). The presence of clinical dementia required for a CERAD and subsequent NIA-Reagan diagnosis was waived in the present study, because all subjects by virtue of inclusion criteria were cognitively normal at death.

For assessment of Lewy body pathology (LBP), the alpha-synuclein mouse monoclonal antibody (Novacaster, Newcastle, UK) immunohistochemistry was used (Jicha et al., 2010; Markesbery et al., 2009). Immunohistochemistry for alpha-synuclein was performed on 10-μm sections that were pretreated with formic acid, blocked in 15% filtered horse serum in automation buffer, incubated with primary antibody for 1 hour, and developed with the

avidin-biotin complex using Nova Red (Vector Laboratories, Burlingame, CA, USA) as the chromogen. The presence or absence of LBP was dichotomized for the present analysis.

Size, location, and histologic age of large and small vessel infarcts were recorded. Microinfarcts, lacunar infarcts, pale infarcts, arteriolosclerosis, cerebral amyloid angiopathy, and hemorrhagic infarcts were counted for each section. Cases in which cerebrovascular pathology was thought to be a significant contributor to antemortem clinical state were indicated by a dichotomous variable based on clinical judgment of the examining neuropathologist, as there are no current rubrics for grading the severity of cerebrovascular pathology with confident correlation to antemortem cognitive parameters.

All pathological diagnoses, semiquantitative staging, and quantitative pathologic counts were performed blinded to clinical data. Once such assessment was made, each case was brought to a neuropathology consensus conference to allow the incorporation of clinical diagnosis required for CERAD and NIA-Reagan diagnostic categorization.

2.3. Application of *PADW* staging criteria using extant neuropathological criteria

The PADW proposed 3 stages of pAD, hypothesized to occur in temporal sequence, that can be directly applied to autopsy specimens derived from subjects who were cognitively intact at the time of death. We applied 2 other pathological categories to define subjects lacking any appreciable AD-related pathology, and those lacking amyloid but with evidence of MTL NFTs that did not fit into the proposed PADW schema (Nelson et al., 2009a). In line with the PADW (Alzheimer's Association, 2010), the pAD stages progress from stage 0 (insufficient number of DPs to satisfy Khatchaturian criteria for AD; Khachaturian, 1985); stage 1, asymptomatic cerebral amyloidosis; stage 2, amyloidosis plus evidence of early neurodegeneration; and stage 3, amyloidosis, evidence of neurodegeneration plus subtle cognitive change. Possibly outside of the AD spectrum were cases that we designated stage 0-N, lacking appreciable DPs (according to the Khachaturian criteria) or NPs, but Braak stage III or IV NFTs (i.e., neurofibrillary pathology predominantly confined to MTL structures). Direct application of these proposed diagnostic stages to neuropathological findings in cognitively intact subjects is operationalized in Table 1.

2.4. Cognitively impaired cases included for comparative analyses

Subjects with documented cognitive deterioration (MCI or early AD) were included if final cognitive testing occurred within 2 years of death. Average interval between final testing and autopsy for all groups was still under 10 months (Table 2). MCI cases ($n = 24$) for this study had a clinical-pathological consensus conference diagnosis (Petersen and Negash, 2008; Winblad et al., 2004) as described above. Subjects with early AD ($n = 14$) had a consensus conference AD diagnosis, met NIA-Reagan criteria for high likelihood of AD (1997), and had Braak stage V pathology (Braak and Braak, 1991b) in addition to meeting CERAD criteria for Definite AD (Gearing et al., 1995).

2.5. Statistical analysis

Unadjusted mean neuropsychological test scores were compared using Student or Satterthwaite *t* test as appropriate, and the overall alpha was preserved at 0.05 using the Bonferroni method. Adjusted means were compared using multiple linear regression. In addition, raw test scores were converted to age-corrected *z* scores based on the baseline performance of the entire normal cohort. Impaired performance on any test was indicated by a *z* score of more than 1.5 standard deviations below the mean (above for Trails A). The proportion of scores indicating impairment in each group was compared using chi-square tests. All analyses were performed using PC-SAS 9.2® or Microsoft Excel®.

Results

Persons who died without detected antemortem cognitive impairments (with final testing within a year of death) were grouped according to autopsy findings into the PADW proposed stages of pAD. Figs. 2 and 3 depict the characteristic pathological findings and distributions of PADW stages in the cohort studied. Fig. 4 shows how individuals in this research cohort fall into each of the pAD stage categories. Note that “stage 0”, without any indication of cerebral amyloidosis, is the largest case category (60/126 or 47%). There are relatively few “stage 1” (13/126, or 10%) with many DPs but few or any NPs. Among the 44 “pure” pAD cases which lack concomitant pathologies, the proportion of cases are — stage 1 (n = 8, 18%); stage 2 (n = 12, 27%); and stage 3 (n = 24, 55%).

Table 2 highlights demographic and neuropathological indexes relevant to each of the PADW stages cases in this series. The groups did not differ on age, education, or gender. ApoEε4 status was proportionally higher in PADW stages 1, 2, and 3 groups than in stage 0 subjects reaffirming the association of ApoEε4 status with cerebral amyloidosis in this series. Quantitative pathology (counted numbers of DPs, NPs, and NFTs in neocortical and medial temporal lobe areas as described in 2. Methods) are also presented in Table 2. Compared with early AD cases, all the pAD categories have in common a lack of appreciable neocortical NFTs. Fig. 3 and Table 3 provide information about the distribution of cases according to the CERAD and Braak staging. Note that most common Braak stage for cognitively intact patients was either Braak III or IV, whereas Braak stage 0 is relatively rarely seen in aged, cognitively intact individuals.

For inclusion in the study, none of the persons designated to represent pAD had antemortem diagnoses of dementia; however, we evaluated whether cognitive assessments could detect group-level differences retrospectively. Results from the last evaluation before death for all groups are presented in Table 4. Note that cognitive assessment results in pAD stages 0-N, 1, stage 2, and stage 3 are not significantly different from stage 0, for any of the tests, even prior to Bonferroni correction. Thirty-six comparisons were made in relation to stage 0 cases (6 variables and 6 groups). The alpha to preserve an overall type I error rate of 0.05 is 0.0014. The lack of significant cognitive differences between pAD groups is also seen when means are adjusted for age, education level, and apolipoprotein E (ApoE) status (data not shown) although some test scores trended down in the stage 3 pAD group (Fig. 5). These results confirm that individuals with a subthreshold burden of AD-type pathology can maintain overall cognitive capacity. However, there were some subtle changes noted on Mini Mental State Examination (MMSE) scores in stage 3 versus stage 0 cases. For subjects without concomitant pathology, the proportion of impaired MMSE scores was significantly higher in stage 3 versus stage 0 (χ^2 = 4.42, p = 0.035, 1 df) as indicated by a z score of more than 1.5 standard deviations below the mean of this group. These data indicate slight differences in MMSE scores relative to the other members of the cohort but are not indicative of clinical MCI. In line with expectations, cases with the clinical diagnosis of MCI or early AD (with Braak stage V pathology) had significantly lower cognitive test scores than any of the pAD cases.

To better define clinical-pathological correlations in pAD stages, we evaluated whether some of the pathological staging criteria are applicable across the full spectrum of cognitive changes. The current criteria for neuropathological diagnosis of AD are linked primarily with neurofibrillary pathology (NPs and NFTs) (1997). We sought to test the correlation between Braak staging and global cognition in our sample that is enriched for cognitively intact individuals. A chart demonstrates the final MMSE scores of individuals in the UK-ADC cohort, stratified by their Braak stage (Fig. 6); these data incorporates also the cognitively impaired dementia. These data demonstrate that decreases in global cognition

(MMSE scores) can only be seen in patients with Braak stage V or VI pathology in this sample. Braak stages I through IV do not provide a robust interval variable that can be correlated with cognitive status in pAD. This is uniform across the other cognitive tests as shown in Table 3.

Concomitant pathologies (LBP and cerebrovascular disease) are relatively frequent in pAD (Table 2). There was a relatively high percentage of cases with incipient non-AD pathologies in pAD stages 1–3 (10/54 = 17.5% of cases). The percentage of cases with concomitant pathologies was even higher in MCI cases (11/23 = 48%) which accords with prior studies (Jicha et al., 2006; Schneider et al., 2009b). Note that more than 10% of the pAD cases had stage 0-N pathology, with MTL NFTs but lacking cortical amyloid plaques (Fig. 7). Only 1 case of hippocampal sclerosis was detected among the cognitively intact individuals.

4. Discussion

Here we provide a neuropathology-based construct to correlate with the preliminary PADW staging criteria, demonstrating that almost half of the cognitively intact subjects in this autopsy series met criteria for stages 1, 2, or 3 pAD. Frequency of pAD pathology progresses from stage 1 or greater (n = 53; 43%) to stage 2 or greater (n = 41; 33%), to stage 3 (n = 26; 21%). Because all the pAD groups had (by definition) intact cognition, and all lack appreciable numbers of neocortical NFTs, these data attest to the importance importance of neocortical NFTs as a key factor in AD pathobiology. However, the presence of some NFTs in hippocampal formation structures is the rule, and not the exception, in cognitively intact older individuals. ApoEε4 genotype is strongly associated with AD-type pathology in pAD, as has been shown for fulminant AD cases in many published clinical and autopsy samples, attesting again to the validity of the PADW construct of pAD stages at least when analyzed from a neuropathological perspective (Jicha et al., 2008). Comorbid pathologies represent a potential confounder to the biomarker-based clinical diagnoses.

Although many cognitively intact subjects lack substantial AD pathology, many others (43%) have at least mild pathology suggesting AD. This observation, which has been made previously (Guillozet et al., 2003; Haroutunian et al., 1999; Price et al., 2009; Schmitt et al., 2000, Thal et al., 2004, Tomlinson et al., 1968), is an important consideration for the PADW staging criteria. While AD-related pathology was present in some cognitively intact individuals, it was far milder in cognitively intact individuals than in AD, confirming that pAD is often associated with a subthreshold level of AD-type pathology. From a diagnostic perspective, it is clear that Braak neurofibrillary stages III–IV do not indicate “intermediate likelihood” of cognitive impairment related to AD pathology when clinical data are unknown. These and other data indicate that neurofibrillary pathology in the neocortex is a key event associated with cognitive decline (Arriagada et al., 1992a; Dolan et al., 2010; Nelson et al., 2009b, 2010a). The Braak staging criteria, with the first 4 stages focused on the hippocampal formation, were adapted for diagnosis of dementia subjects, but have not been validated for use in samples covering the full spectrum of disease. An increased focus on the pattern of neocortical NFT development may be merited (Markesbery et al., 2006; Nelson et al., 2009b). Correlations in our sample between Braak staging and MMSE scores more closely resemble some previously published series (Whitwell et al., 2008) than others (Jellinger and Attems, 2007b). This may reflect differences in diagnostic thresholds and also the relatively large number of clinically well-characterized, cognitively intact individuals in our sample.

The presence of DPs (stage 1) does not correlate with antemortem cognitive function in our cohort (Table 3), nor is there a substantial group of demented individuals in the UK-ADC

autopsy series with DPs only (data not shown). The “Khachaturian criteria” for AD diagnosis (Khachaturian, 1985), based on DP, has been removed from AD diagnostic relevance for over a decade, and our data provide no fresh impetus to revive DP-based neuropathological diagnoses for the detection of clinically evident AD. However, for the purposes of identifying patients with pAD, at risk for eventually developing full-blown AD, and in the context of biomarker development, the presence of DPs alone (stage 1) may be directly relevant. There was subtle cognitive impairment detected in the stage 3 pAD using age-corrected *z* scores to study MMSE test results. These data are compatible with the PADW criteria that stage 3 cases have “subtle cognitive deterioration”. Because these cases also (by our definition) have Braak stages above II, they also satisfy the criteria of including “markers of neurodegeneration” as NFTs correlate relatively well with cell loss in AD brain (Giannakopoulos et al., 2003).

The present study also considers NFT-predominant pathology that is not well defined using the current NIA-Reagan classification system (1997, Nelson et al., 2010b). We recently described a group of autopsied patients with hippocampal NFTs but without neocortical NP, referred to as stage 0-N in the current study (Nelson et al., 2009a), which raises the question of multiple convergent pathological processes in the development of AD-type pathology. It is not known how these cases relate to the disease “tangle-predominant dementia” (Jellinger and Attems, 2007a), because these cases lack dementia and we did not find patients in our series with tangle-predominant dementia (Nelson et al., 2009a). What is clear is that NFT and amyloid plaques can develop, albeit moderately, in the absence of each other. Although many published studies suggest that NFTs are most directly associated with cell/synaptic injury in AD, NFTs are also seen in many neurodegenerative conditions, in contrast to NPs that are specific to AD (literature reviewed in Nelson et al., 2009b).

Diagnostic accuracy in pAD is critically dependent on the identification of other prevalent diseases linked to brain aging. The findings of cerebrovascular disease (CVD) and LBP in a subset of cognitively intact subjects demonstrate that, like AD, these pathologic findings exist in a preclinical state. The antemortem detection of preclinical cerebrovascular disease is possible with the use of MRI, computerized tomography (CT) scans, and vascular imaging techniques such as angiography and Doppler studies (de Leon et al., 2007; Hachinski et al., 2006; Kalaria et al., 2008; Prins et al., 2004; Yoshita et al., 2006; Zekry et al., 2002). The confident detection of preclinical dementia with Lewy bodies (DLB) is not yet achievable, but previous work demonstrated that predementia stages of dementia with Lewy bodies may be detectable through the recognition of early cognitive and importantly noncognitive symptoms (Jicha et al., 2010; Molano et al., 2010).

Hippocampal sclerosis is a prevalent neurodegenerative disease (~10% of aged brains) that causes hippocampal atrophy and cognitive impairment (Nelson et al., in press), and which raises some questions about the use of MRI-detected hippocampal atrophy as a specific biomarker for AD (Attems and Jellinger, 2006; Hua et al., 2008; Potkin et al., 2009). In fact, both hippocampal sclerosis and FTLD may show reduced MTL volumes early in the disease course (Chertkow and Black, 2007; de Leon et al., 2007). Only 1 pAD case had hippocampal sclerosis pathology, although 12.5% in the MCI subjects did, indicating that hippocampal sclerosis, when present, induces cognitive impairment as shown previously (Dickson et al., 1994; Nelson et al., 2010a).

The difficulty in detecting pAD clinically, at least cross sectionally, highlights the need for development of accurate biomarkers to detect the biological processes in AD that eventually lead to overt clinical decline and dementia (Albert et al., 2001; Chong and Sahadevan, 2005; Hulette et al., 1998; Jobst et al., 1997; Schmitt et al., 2000; Tierney et al., 1996, 2005; Watson et al., 2005). The disease process clearly begins years before the development of

clinical symptoms (Arriagada et al., 1992b; Bennett et al., 2006; Braskie et al., 2010; Davis et al., 1999; Haroutunian et al., 1998; Hulette et al., 1998; Knopman et al., 2003; Morris and Price, 2001; Schmitt et al., 2000; Troncoso et al., 1996). Inevitably, a substantial proportion of "normal" control subjects have incipient AD, which is a relevant consideration for the design of research studies comparing normal and AD groups (Becker and Greig, 2008; Cummings et al., 2007; Sabbagh, 2009).

Much work remains to be done given our present level of diagnostic certainty in diverse cohorts. Cerebrospinal fluid (CSF) amyloid levels may not distinguish pAD from LBD in cognitively intact individuals given the prevalence of amyloid pathology in dementia with Lewy bodies (Aarsland et al., 2008; Clark et al., 2003; Gómez-Tortosa et al., 2003; McKeith, 2006; McKeith et al., 1998; Mollenhauer et al., 2005a, 2005b; Vanderstichele et al., 2006). On the other hand, CSF tau and phospho-tau may be reliable discriminators of these pathological disease states in "pure" disease states (Aarsland et al., 2008; Clark et al., 2003; Gómez-Tortosa et al., 2003; Mollenhauer et al., 2005a, 2005b; Vanderstichele et al., 2006) but may not enable the identification of individuals with stage 0-N pathology. Amyloid ligand-PET may fall short of identifying PADW stage 1 subjects (13/126 cases in the current series) given the low affinity of some existing amyloid ligands for DP pathology, although developments in this area appear promising as ligand binding is more fully characterized and new compounds are developed (LeVine, 2005; Lockhart et al., 2007; Thompson et al., 2009).

The good news is that the lack of AD-type pathology in many aged individuals (stage 0 and stage 0-N cases, 57% of cognitively intact persons, average age 82.6 years at death) argues that the eventual development of even mild-to-moderate AD pathology is not inevitable. There is no way to ever prove this as death in the absence of AD pathologynegates the longitudinal follow-up required to fully address this issue. Nonetheless, healthy cognitive and pathological aging appears to be an achievable goal, although the lifestyle, medical, and genetic factors allowing such a favorable pathological outcome are unknown at the present time. Identification of such factors may enable future development of effective preventive strategies for AD.

Limitations of this study include a potential inability to generalize the findings to more disparate racial and socioeconomic groups. The studied cohort, a convenience sample, is almost exclusively Caucasian and well educated (Schmitt et al., 2001). There are always biases in an autopsy sample because there never is a truly epidemiological autopsy cohort in the sense of representing without bias all members of the overall population (Zaccai et al., 2006). Because the research volunteers in the current study were motivated to be seen within a year of death, this could indicate some differences from the general population. Another issue with our dataset is the problem of missingness: not all subjects participated in every cognitive assessment because the standard battery of tests has changed over time. Further, some of the research volunteers died before or during the evolving conceptualization of clinical MCI diagnosis (Petersen et al., 2001; Winblad et al., 2004). This problem was minimized but not negated by the use of chart-based retrospective identification of some MCI patients (Jicha et al., 2010).

Another inherent shortcoming of the present study is that we did not assess all aspects of biomarkers and the pathobiology of AD in these subjects. A wealth of data supports the role of oxidative stress, inflammation, neurotransmitter alterations, synaptic loss, and other pathological neuronal changes (i.e., TDP-43, see Fig. 6) in dementia. Our focus on DPs, NPs, and NFTs in the present study in no way implies that other biochemical alterations lack importance in the development and biomarker-based detection of pAD. Further work defining the potential mechanisms in the disease process is needed.

The strengths of this study lie in the large number of clinically well-characterized, cognitively normal subjects tested cognitively near autopsy and the detailed, quantitative, neuropathologic analysis allowing the characterization of pAD staging and comparison with clinically evident AD. Assessment of non-AD pathologies, including stage 0-N cases, may have relevance to biomarker studies. The stagebased groupings that we used, in correlation to the PADW preliminary recommendations, were based on presumed correlations between biomarkers and neuropathological findings, and these will require further refinement in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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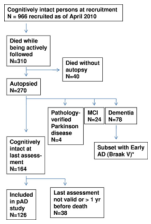

Fig. 1.

Flow chart to demonstrate the individuals included and excluded in the assessment of preclinical Alzheimer's disease (pAD) in correlation with the pAD Workgroup recommendations (Alzheimer's Association, 2010). Note that all individuals with eventual diagnosis of pAD or mild cognitive impairment (MCI) were recruited while initially cognitively normal. * Of the 14 individuals included as early Alzheimer's disease (AD; Braak stage V), 12 were recruited while neurologically normal but 2 were cognitively impaired when recruited.

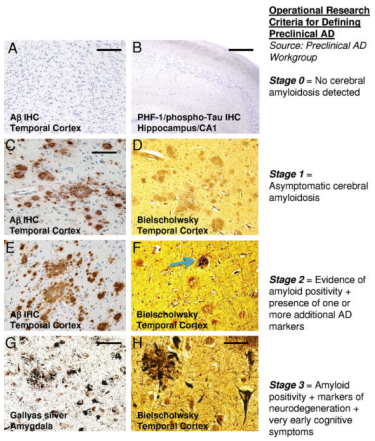

Fig. 2.

Representative histopathological features that may correspond with the evolution of preclinical Alzheimer's disease (pAD) in correlation with the preliminary recommendations of the Preclinical Alzheimer's Disease Workgroup (stages described at right). Stage 0 (A and B) refers to cases without cerebral amyloidosis. There are no amyloid plaques —(A) using Aβ immunohistochemistry (IHC) — or neurofibrillary changes — (B) PHF-1/ phospho-tau IHC in a low-power photomicrograph of hippocampal CA1 (counterstained with hematoxylin). In stage 1, there are diffuse amyloid plaques, detectable using Aβ IHC (C), but these plaques lack neuritic component that would be detectable using a Bielschowsky silver stain (D). In stage 2, there are both diffuse amyloid plaques (E) and also some plaques with a neuritic component (blue arrow in F). By stage 3, there are typically features seen in fulminant Alzheimer's disease (AD), but with lower densities especially in the neocortex. Medial temporal lobe regions such as the amygdala (G) may have many neuritic amyloid plaques and tangles as shown here with a sensitive Gallyas silver stain. However, one usually does not see many neuritic amyloid plaques in the neocortex (upper left of H) without also seeing some neurofibrillary tangles (lower right of H). Scale bars: (A) 500 μm; (B) 1 mm; (C–F) 100 μm; (G) 50 μm; (H) 30 μm.

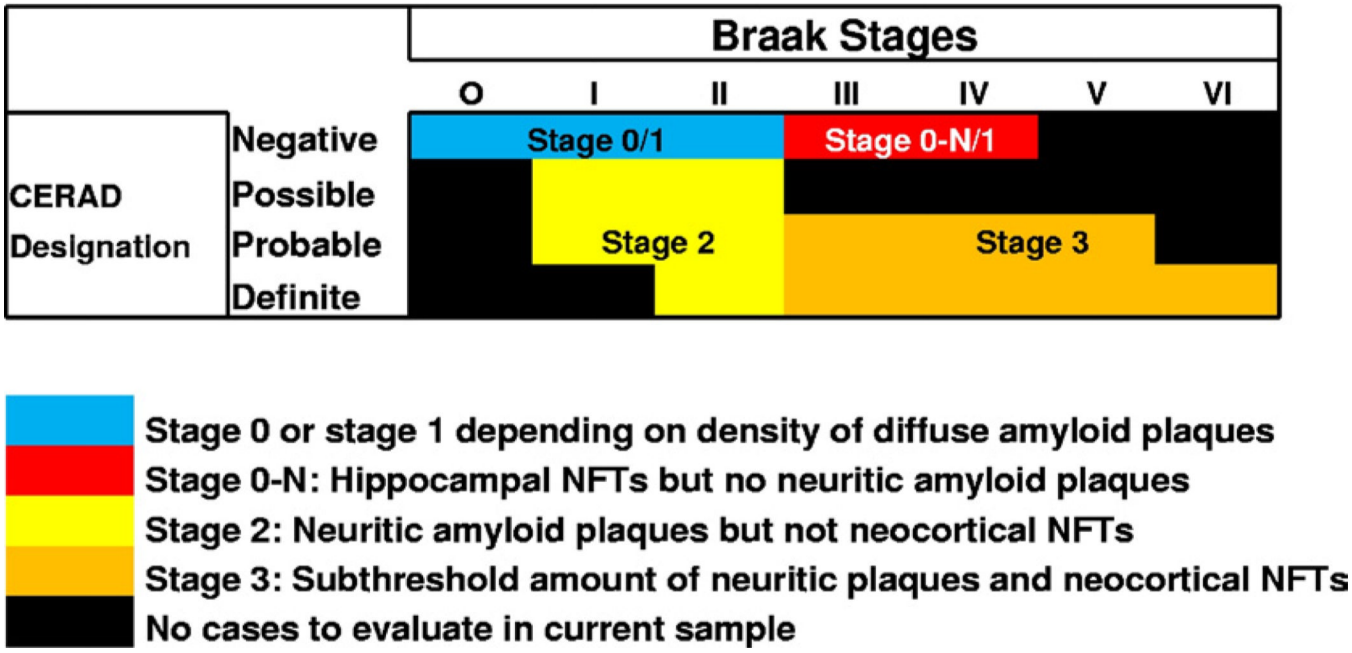

Fig. 3.

Grid with information related to how patients were classified in the current study. Only patients that died while cognitively intact with cognitive testing within a year of death were included in this study and have results that are relevant to this chart. The grid shows that individual patients can be categorized according to the extent of neurofibrillary pathology using the Braak staging. Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores provide information about the density of neuritic amyloid plaques. In the earliest part of the disease, without either neurofibrillary tangles or neuritic amyloid plaques (blue portion of the chart), a case is determined to be stage 0 if there are no diffuse plaques but a case is stage 1 if the brain has enough diffuse amyloid plaques to meet the Khachaturian criteria (Khachaturian, 1985). Stage 0-N refers to cases with a modicum of neurofibrillary tangles in the hippocampus, without amyloid plaques in neocortex, as described in a prior study (Nelson et al., 2009a).

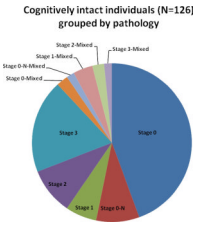

Fig. 4.

Pie chart shows relative numbers of cases that fall into each of the preclinical Alzheimer's disease (pAD) stages (total *n* = 126). A relatively large proportion of are "stage 0" (59/126, or 47%) which indicates no cortical amyloidosis. Cases with diffuse plaques but lacking substantial numbers of neuritic plaques ("stage 1") are relatively few. Cases with mixed" pathology were found in 10/54 (19%) of stage 1–3 pAD cases, indicating subclinical levels of cerebrovascular disease, cortical Lewy bodies, or hippocampal sclerosis.

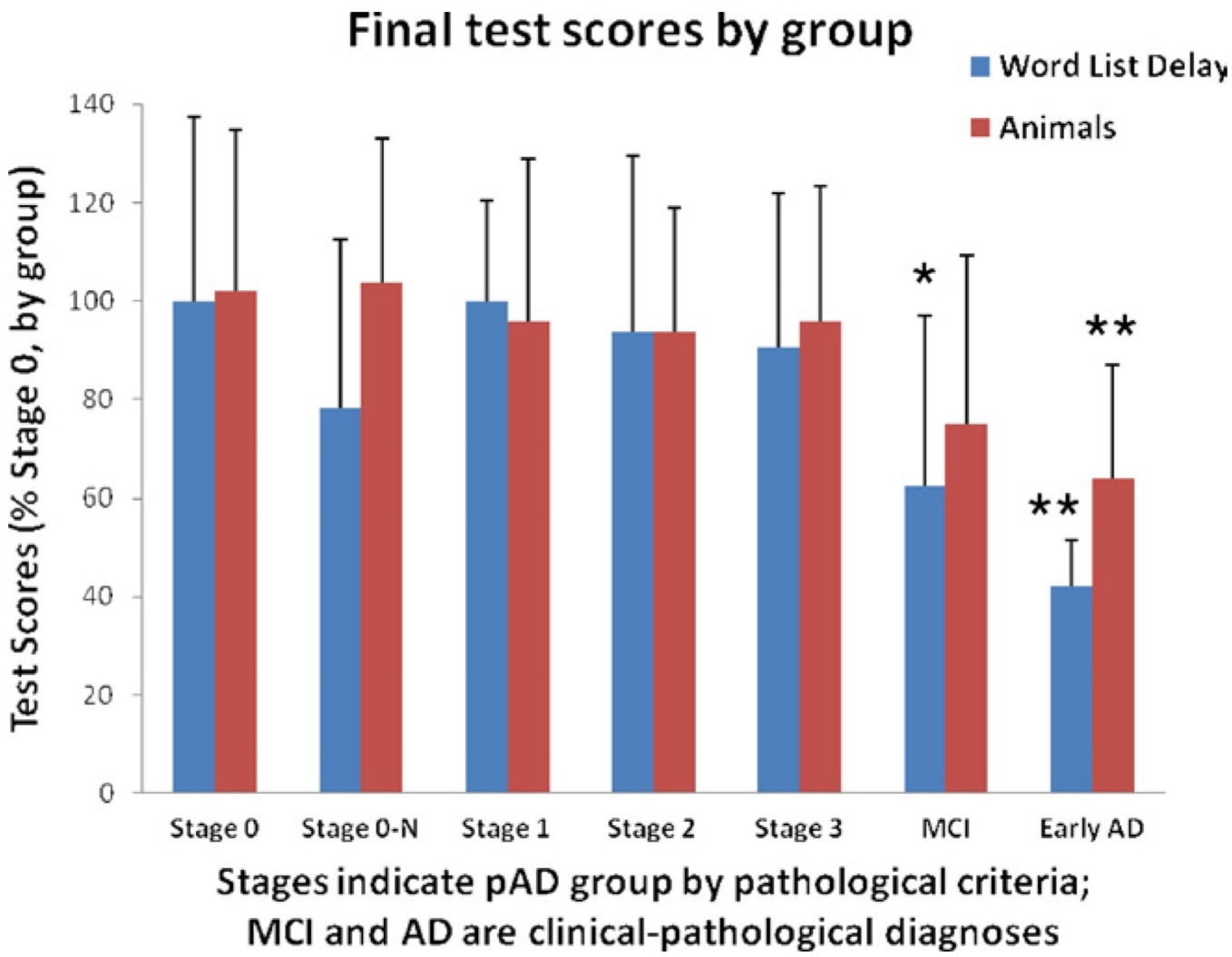

Fig. 5.

Groups in the different preclinical Alzheimer's disease (pAD) stages lack significant differences on many cognitive tests. Shown here are results for Logical Memory: Immediate Recall and Animal Fluency sections of the Universal Dataset test battery. Error bars = standard deviation. All cases with pAD were tested within a year of death. * $p < 0.05$ or ** $p < 0.001$.

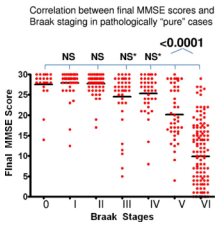

Fig. 6.

Early Braak stages are not helpful interval variables in the context of preclinical or early Alzheimer's disease (AD). Shown here is a chart of final Mini Mental State Examination (MMSE) scores plotted in correlation with Braak staging of neurofibrillary degeneration. From an initial sample of University of Kentucky Alzheimer's Disease Center (UK-ADC) autopsies that included demented and nondemented subjects (n = 612), cases were excluded that had frontotemporal dementia pathology, alpha-synucleinopathy such as dementia with Lewy bodies, vascular dementia, and any case that lacked Braak staging or MMSE scores. Cases were not excluded from this analysis based on interval between final MMSE test and death. Although in a person with documented dementia, a Braak stage less than V may indicate some impact from the disease, this ordinal variable cannot confidently predict global cognitive status in the earliest stages of Alzheimer's disease. This is probably because cognitive impact from AD pathology may be difficult to detect before there are abundant neocortical neurofibrillary tangles (NFTs) (Arriagada et al., 1992a). p values show result of comparing mean MMSE scores in each Braak stage versus Braak stage 0 using unpaired Student t test. NS, not significant; NS*, average final MMSE scores trended lower for Braak stage III and IV ($p \sim 0.04$), but this was not significant after correction for multiple comparisons.

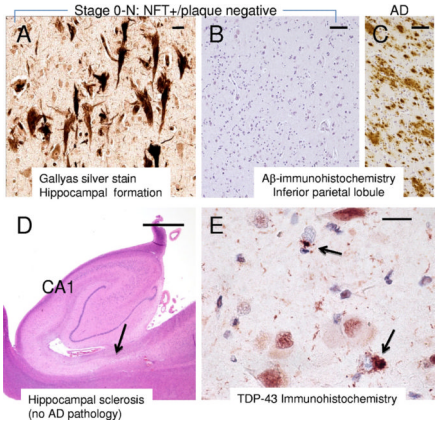

Fig. 7.

Some prevalent brain pathologies in older individuals do not map well onto the preliminary Preclinical Alzheimer's disease Workgroup (PADW) recommendations. Brains with medial temporal lobe neurofibrillary tangles (NFTs) but no amyloid plaques in the cortex, which we refer to as stage 0-N, comprise over 10% of preclinical Alzheimer's disease (pAD) cases (A and B). This brain from a 78-year-old male (final Mini Mental State Examination [MMSE] score = 29) showed moderate densities of NFTs in the hippocampal formation and entorhinal cortex (A, stained with Gallyas stain) but there was no Aβ-positive plaques detected (B), in contrast to what is seen in Alzheimer's disease (AD) brains using the same stain (C, at same magnification). Whereas stage 0-N was seen in 13/126 cognitively intact individuals, we found only a single case with hippocampal sclerosis in nondemented individuals, so this form of non-AD hippocampal atrophy appears more relevant to mild cognitive impairment and demented states. (D) An hematoxylin and eosin stained brain from an 88-year-old female with Clinical Dementia Rating (CDR) = 1 and clinical diagnosis of presumed early AD. The hippocampus appears shrunken, especially the subiculum (arrow). Immunohistochemical stain for TDP-43 (E; nuclei counterstained with hematoxylin) showed aberrant pattern of staining with cytoplasmic TDP-43 inclusions (arrows). Scale bars: (A and E) 25 μm, (B and C) 100 μm; (D) 2 mm.

Table 1

Application of the PADW stages to neuropathological findings at autopsy in cognitively intact subjects

	Neuropathological findings			
Stage	**Khatchaturian (DPs)**	**CERAD (NPs)**	**Braak (NFTs)**	**Rationale and considerations**
Stage 0	No	Negative	0–II	Absence of measurable pathology that might be reflected in positive antemortem biomarker results.
Stage 1	Yes	Negative	0–II	Cerebral amyloidosis may be detected using CSF amyloid measures and to a lesser degree, amyloid-PET ligand binding, although current amyloid-PET ligands may not bind DP giving false negative results in this stage.
Stage 2	Yes	Possible, probable, or definite	0–II	Cerebral amyloidosis may be detected using CSF amyloid measures and amyloid-PET ligand binding. Medial temporal lobe atrophy and positive CSF tau/p-tau provide evidence for early neuronal degeneration.
Stage 3	Yes	Probable or definite	III, IV, V, or VI	NFT density is typically milder in neocortex than in clinically evident AD. Criteria for “subtle cognitive change” accounted for by modest NFT accumulation in neocortex. The authors acknowledge that MTL NFT seen in stage 2 of these operational criteria may be sufficient to produce “subtle cognitive change” in memory tests and so overlap between these stages is unavoidable.
Stage 0-N	No	Negative	III or IV	Although this group does not map readily on to the PADW staging, they are relevant to the discussion because they have some pathology (which may be detected using CSF biomarkers) without necessarily belonging on the AD continuum, as described previously (Nelson et al., 2009a).

Key: AD, Alzheimer’s disease; CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; CSF, cerebrospinal fluid; DPs, diffuse plaques; MTL, medial temporal lobe; NPs, neuritic plaques; NFTs, neurofibrillary tangles; PADW, Preclinical Alzheimer’s Disease Workgroup; PET, positron emission tomography.

Table 2

Demographic, genetic (ApoE), and neuropathological features of study groups

Demographics and ApoE alleles	Stage 0 (*n* = 59)	Stage 0-N (*n* = 13)	Stage 1 (*n* = 13)	Stage 2 (*n* = 15)	Stage 3 (*n* = 26)	MCI (*n* = 24)	Early AD (*n* = 14)
Age at death	81.6 ± 8.7	87.6 ± 5.2	84.5 ± 8.5	83.9 ± 5.9	86.1 ± 6.3	89.1 ± 4.3	89.8 ± 5.9
Sex (% male)	49.2	61.5	38.5	40	50	40.9	35.7
Education	60.0 ± 2.5	15.8 ± 2.4	15.6 ± 3.3	17.0 ± 1.8	15.8 ± 2.2	16.3 ± 2.3	14.2 ± 3.0
ApoE4+ (%)	7.1	16.7	41.7	46.7	24.0	31.8	53.8
MTL DPs, counted	0.6 ± 1.8	1.3 ± 3.1	5.5 ± 4.9	8.0 ± 4.8	7.2 ± 6.3	6.5 ± 7.2	13.2 ± 5.5
MTL NPs, counted	0.04 ± 0.2	0.2 ± 0.4	1.7 ± 1.8	2.5 ± 2.3	4.0 ± 3.1	1.6 ± 1.9	3.7 ± 2.4
MTL NFTs, counted	3.1 ± 4.9	22.3 ± 18.6	5.3 ± 4.3	4.5 ± 4.5	16.4 ± 9.0	17.4 ± 20.3	42.1 ± 19.0
NeoCx DPs, counted	2.4 ± 4.6	2.2 ± 6.1	36.2 ± 10.8	28.7 ± 9.9	32.7 ± 9.5	21.3 ± 17.7	37.3 ± 8.6
NeoCx NPs, counted	0.4 ± 1.0	0.2 ± 0.5	1.6 ± 1.2	8.0 ± 4.7	12.0 ± 6.3	8.4 ± 5.8	14.8 ± 5.3
NeoCx NFTs, counted	0.1 ± 0.2	0.4 ± 0.5	0.3 ± 0.4	0.1 ± 0.2	2.1 ± 2.6	1.3 ± 3.1	6.7 ± 3.9
Cortical Lewy bodies (%)	1.7	0	15.4	0	3.9	12.5	0
Hippocampal sclerosis (%)	1.7	0	0	0	0	12.5	0
Cerebrovascular pathology (%)	1.7	15.4	30.8	20	3.9	29.2	21.4

Individuals tested within a year of autopsy with preclinical AD (pAD), MCI, and early AD were the basis of this study. All individuals in stages of pAD (stages 0–3) were tested within a year of death (*n* = 126). “NeoCx” counts refer to summed neocortical counts from inferior parietal, occipital, temporal, and frontal neocortical regions as described in 2. Methods. “MTL” counts refer to summed medial temporal lobe counts from hippocampal CA1, subiculum, entorhinal cortex, and amygdala. Note that pAD cases tend to have few, if any, neocortical NFTs. Individuals who die with clinical diagnosis of MCI tend to have exclusive or comorbid non-AD pathologies. Thus, the mean counted AD lesions are lower because some MCI cases are, for example, hippocampal sclerosis only. All cases with “early AD” are Braak stage V.

Key: AD, Alzheimer’s disease; ApoE, apolipoprotein E; DPs, diffuse amyloid plaques; MCI, mild cognitive impairment; MTL, medial temporal lobe; NFTs, neurofibrillary tangles as described in 2. Methods; NPs, neuritic amyloid plaques.

Table 3

Numbers of "pure" pathology cases according to CERAD and Braak stages (n = 111)

	Braak stages						
	0	**I**	**II**	**III**	**IV**	**V**	**VI**
CERAD Designation							
Negative	13	25/1[a]	18/4a	6/2[a]	5/1[a]	0	0
Possible	0	1	3	0	0	0	0
Probable	0	1	5	6	6	3	0
Definite	0	0	2	1	4	3	1

The number of cases without appreciable concomitant pathologies in the present study. All cases had autopsies within a year of final clinical evaluation. Total n = 111. Note that cases with concomitant pathologies (n = 15) were not included in this table. The exceptional case with Braak stage VI and presumed preclinical AD has been described before (Nelson et al., 2009b).

Key: AD, Alzheimer's disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; PADW, Preclinical Alzheimer's disease Workgroup.

[a]Cases without diffuse plaques/cases with diffuse plaques (i.e., PADW stage 1).

Table 4

Cognitive test scores of study groups; cases with and without concomitant pathologies

	Stage 0	*n*	Stage 0-N	*n*	Stage 1	*n*	Stage 2	*n*	Stage 3	*n*	MCI	*n*	Early AD	*n*
Including cases with concomitant pathologies														
MMSE	28.4 ± 1.4	59	27.7 ± 2.5	13	28.5 ± 1.5	13	28.7 ± 1.7	15	27.6 ± 2.3	26	26.0 ± 3.1****	23	20.6 ± 8.7****	14
Animals	16.4 ± 5.5	58	16.6 ± 4.4	13	16.2 ± 5.2	13	14.4 ± 4.4	15	15.9 ± 4.5	26	12.9 ± 5.6*	20	10.7 ± 3.7***	11
Trails A	54.0 ± 29.2	51	55.1 ± 18.0	10	48.8 ± 14.2	13	56.9 ± 47.6	14	51.5 ± 21.1	22	66.8 ± 37.2	16	98.8 ± 34.4****	10
Log mem immediate	14.7 ± 4.5	54	14.4 ± 4.1	12	14.3 ± 2.9	13	14.5 ± 4.0	13	14.3 ± 3.8	24	10.7 ± 3.9***	19	6.4 ± 4.9****	9
Praxis	9.2 ± 1.0	43	9.2 ± 0.9	10	9.5 ± 1.1	13	9.0 ± 1.3	13	8.8 ± 0.9	19	8.6 ± 2.3	11	8.4 ± 1.3	5
Word list delay	6.4 ± 2.4	48	5.2 ± 2	11	6.4±1.4	13	5.6 ± 2.1	11	5.9 ± 2.0	21	4.6 ± 2.1*	13	3.8 ± 1.9****	5
Time since last eval (days)	184.1 ± 105.6	59	213.7 ± 96.8	13	234.2 ± 101.0	13	192.6 ± 88.9	15	192.9 ± 108.4	26	318.5 ± 163.5****	24	285.0 ± 174.4	14
Cases lacking concomitant pathologies														
MMSE	28.4 ± 1.3	56	27.5 ± 2.7	11	28.8 ± 1.4	8	28.8 ± 1.7	12	27.5 ± 2.3	24	26.3 ± 2.3**	12	20.4 ± 8.7*	11
Animals	16.6 ± 5.4	55	16.9 ± 4.8	11	15.6 ± 5.4	8	15.3 ± 4.1	12	15.6 ± 4.5	24	12.2 ± 5.6*	10	10.4 ± 3.8***	9
Trails A	53.5 ± 29.8	48	54.3 ± 19.7	8	43.8 ± 21.4	8	43.8 ± 13.9	11	52.8 ± 21.6	20	70.6 ± 39.8**	9	107.1 ± 33.9****	7
Log mem immediate	14.7 ± 4.6	51	13.6 ± 3.9	10	14.8 ± 2.7	8	14.5 ± 3.8	11	14.1 ± 3.9	22	12.2 ± 3.8*	10	4.9 ± 3.9****	7
Praxis	9.2 ± 1.0	40	9.1 ± 1.0	8	10.0 ± 0.8*	8	9.3 ± 1.1	10	8.8 ± 0.9	18	8.5 ± 2.9	6	9.0 ± 0.0	3
Word list delay	6.4 ± 2.4	45	5.0 ± 2.2	9	6.4 ± 1.3	8	6.0 ± 2.3	8	5.8 ± 2	20	4.0 ± 2.2*	7	2.7 ± 0.6**	3
Time since last eval (days)	181.1 ± 107.6	56	211.9 ± 98.3	11	244.5 ± 86.2	8	196.7 ± 99.2	12	191.8 ± 112.4	24	323.8 ± 168.2*	13	268.1 ± 168.6	11

Cognitive test scores in all 7 groups with or without inclusion of concomitant pathologies. *p* values represent the results of unadjusted Student *t* test or Satterthwaite *t* test as appropriate, comparing results from that group relative to Stage 0 (minimal or no AD-type pathology) pAD group.

Key: AD, Alzheimer's disease; eval, evaluation; Log mem, logical memory; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; pAD, preclinical Alzheimer's disease.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.005$.

**** $p < 0.001$.