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"Preclinical" AD revisited

Neuropathology of cognitively normal older adults

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Article abstract—*Objective:* To classify neuropathologic alterations in the brains of nondemented older adults using current sets of criteria for AD. *Background:* AD neuropathologic alterations are found in the brains of some nondemented elderly subjects and suggest the possibility of presymptomatic AD. Three sets of guidelines have been developed to classify AD using senile plaques, neuritic plaques, and neurofibrillary tangles (NFT). *Methods:* Neuropathologic changes in 59 older adults followed longitudinally with a standard battery of mental status measures were investigated using Khachaturian, Consortium to Establish a Registry for Alzheimer's Disease (CERAD), and National Institute on Aging–Reagan Institute (NIA-RI) guidelines. AD neuropathologic markers were evaluated in neocortical and allocortical regions. Cases were categorized as neuropathologically "normal" or "AD-like" and compared for possible mental status differences. *Results:* Between 11 and 49% of cases met one or more of the three classifications of AD. With adjustments for multiple comparisons, only NFT in hippocampal CA1 region were associated with autopsy age, suggesting that this may represent a pathologic process associated with normal brain aging. Using the NIA-RI guidelines, subjects in the AD-like group performed less well on the immediate paragraph recall and word-list delayed recall than their counterparts who did not meet these guidelines. *Conclusions:* These data indicate that the prevalence of "preclinical" AD in our population is relatively low based on the NIA-RI classification. Although many subjects had AD-like changes based on CERAD and Khachaturian guidelines, they exhibited no differences in mental performance, suggesting that the aging brain may be able to withstand such structural changes without meaningful impact on mental functioning.

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The histopathologic alterations in the brains of patients with AD consist of neurofibrillary tangles (NFT) and senile plaques (SP). These entities accumulate most prominently in the entorhinal cortex, hippocampus, amygdala, and cerebral neocortex. Two widely used guidelines for the histopathologic diagnosis of AD depend heavily on the presence of SP. The Consortium to Establish a Registry for AD (CERAD) guidelines[1] use semiquantitation of neuritic plaques (NP), whereas the guidelines described by Khachaturian[2] use quantitation of SP of any type plus some NFT. Recently, a third set of guidelines for the neuropathologic diagnosis of AD that focuses on NP and NFT was proposed by The National Institute on Aging–Reagan Institute (NIA-RI).[3]

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and then scroll down the Table of Contents for the August 8 issue to find the title link for this article.

The brains of many nondemented elderly individuals contain variable numbers of SP, which has been referred to as "pathologic aging," a term referring to a form of senile cerebral amyloidosis not associated with overt clinical manifestations.[4-8] Although neuro-

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pathologic changes in persons older than 55 years often demonstrate the presence of at least a few SP and NFT,[9] and SP may increase as a function of advancing age,[10] some data suggest that SP accumulation is not inevitably related to "normal" aging.[11] Other studies have reported elderly individuals with normal intellectual functions whose brains contained sufficient numbers of SP and NFT to meet at least one set of neuropathologic guidelines for the diagnosis of AD.[12,13] Many of these brains contain abundant diffuse plaques (DP), thought by some to be the forerunner of NP.[14] Several of these studies relied on retrospective evaluations or medical chart review for the presence or absence of clinical manifestations of AD,[10,15] whereas others relied on limited mental status assessments obtained before death.[16] Thus, the clinicopathologic correlations in these subjects are less than ideal, leaving open the question of the relationship between pathologic aging and early or presymptomatic AD.

Several notable exceptions to the limited premortem assessment of cognition and neuropathologic changes in brain have appeared in the literature.[12,13,17-21] Data from the Washington University Memory and Aging project[12,13,17,18] suggest that persons with a Clinical Dementia Rating (CDR)[22] score of 0.5 (questionable dementia) at some point during their lives develop neuropathologic changes consistent with AD and that associations between measures of cognition and neuropathologic findings exist.[12,23] Similar data from the Mount Sinai AD Center[20,21] suggest AD changes in the brains of normal elderly are relatively common and appear to be associated with dementia severity and possibly with changes in cognition in clinically nondemented older adults. This has led to the concept of "preclinical AD" for some community dwelling and functional older adults.

This report describes the relationship between the current neuropathologic criteria used in the postmortem diagnosis of AD and mental status test findings in a series of older adults who were evaluated prospectively as part of our normal brain aging study.

Methods. *Subjects.* Fifty-nine older adults enrolled in a study of normal aging were examined at autopsy. These autopsies were the first obtained from a group of 400 older adults who agreed to undergo annual mental status examinations, complete neurologic and physical examinations every other year, and donate their brains at death. This group of older adults was recruited by letter and telephone contact from a volunteer pool of approximately 4000 individuals maintained by the Sanders-Brown Center on Aging. This volunteer pool initially was developed from a list of registered voters age 60 years and over in the Lexington, KY area. Other volunteers were then recruited through local media coverage of the research activities of the University of Kentucky AD Research Center (ADRC) and from personal referrals by individuals already enrolled in the project.

The inclusion criteria for this project (on enrollment) were: 1) absence of National Institute for Neurological and Communicative Disorders and Stroke–Alzheimer's Disease[24] and Related Disorders Association criteria for AD[24]; 2) absence of medical and psychiatric conditions that affect cognition and age greater than 60 years; 3) initial mental status examination scores above standard clinical cutpoints for dementia (e.g., Mini-Mental State Examination [MMSE] $>$ 24); 4) willingness to complete annual mental status examinations; and 5) brain donation at death.

Tissue sampling and processing. Brains for this study were obtained from 27 men and 32 women. Postmortem intervals ranged from 1.7 to 23.4 hours, with a mean of 3.5 hours (only two cases had a postmortem interval greater than 6 hours). The known causes of death were cancer (n = 9), myocardial infarction (n = 11), pulmonary insufficiency and emboli (n = 2), bowel perforation (n = 3), and acute cerebellar and cerebral hemorrhage (n = 2). Only two subjects had abnormalities on gross brain examination. One had an acute cerebellar hemorrhage with tonsillar herniation and another had a large acute cerebral hemisphere hemorrhage with uncal herniation. These changes did not affect routine staining or immunohistochemistry.

Specimens from each brain were taken from the middle frontal gyrus (Brodmann area 9), superior and middle temporal gyri (areas 21 and 22), inferior parietal lobule (areas 39 and 40), occipital lobe (areas 17 and 18), hippocampus (CA-1), entorhinal cortex, amygdala, basal ganglia, nucleus basalis of Meynert, thalamus, midbrain, pons, medulla, and cerebellum, and processed in the standard manner. Sections were cut at 8 μm and stained with hematoxylin-eosin, the modified Bielschowsky method, and the Gallyas stain, and 10-D-5, ubiquitin, and alpha-synuclein immunohistochemistry.

NFT and SP quantification. SP and NFT counts were determined on Bielschowsky-stained sections of the middle frontal gyrus, middle temporal gyrus, inferior parietal lobule, occipital area 18, hippocampal CA-1, amygdala, and entorhinal cortex. SP were counted using a 10$\times$ objective (2.35 mm^2) in the five most involved fields in each section of the above regions. Fewer fields were counted in CA-1 because of the small size of this structure. SP were separated into DP (plaques without neurites) and NP (plaques with neurites) in each region. NFT were counted with a 20$\times$ objective (0.568 mm^2) in the five most involved fields of each section of the above regions. An arithmetic mean was calculated from the counts of the five most involved fields for DP (DP/2.35 mm^2), NP (NP/2.35 mm^2), and NFT (NFT/0.558 mm^2) for each region. Neuropathologic diagnosis was then made using the guidelines proposed by Khachaturian,[2] CERAD,[1] and NIA-RI.[3] Participants were classified as "normal" and "AD-like" using these three sets of criteria. A more comprehensive review of the neuropathologic findings in these subjects has been reported.[25]

Mental status examinations. The assessment of cognition in these volunteers was completed on an annual basis. Tests of cognition were selected to provide data that would be comparable to other ADRC projects on normal aging and dementia and therefore incorporated some of the tests from the Washington University ADRC,[12] screening tests for AD used by Eslinger et al.,[26] and the mental status procedures of CERAD.[27] These mental status examinations were supplemented by standard psychological tests that were administered on enrollment including the Vocabulary and Digit Symbol subtests from the Wechsler Adult Intel-

Table 1 *Mental status test battery*

Measure	Function
Mini-Mental State Examination*	Global mental status
Blessed Information-Memory-Concentration Test*	Global mental status
Temporal Orientation Test*	Orientation to time
Wechsler Memory Scale Mental Control*	Attention and concentration
Logical Memory (Wechsler Memory Scale)*	Verbal learning; immediate recall
Benton Visual Retention Test‡	Visual memory
Word list learning and recognition from the Alzheimer's Disease Assessment Scale (ADAS)*	Verbal learning, memory, delayed recall (savings)
Verbal Fluency (Controlled Oral Word Association)*	Language and semantic memory
Animal naming (Boston Diagnostic Aphasia Examination)*	Language and semantic memory
Boston Naming Test (15 items)*	Confrontation naming
Vocabulary subtest (Wechsler Intelligence Scale)†	Premorbid ability
Digit Symbol (Wechsler Intelligence Scale)†	Speeded processing
Trailmaking test (Halstead–Reitan Battery)*	Visual scanning, tracking, attention, flexibility
ADAS design reproduction*	Constructional praxis

* Baseline and annual assessment.
† Baseline only.
‡ Biannual testing.

ligence Scale–Revised[28] and the Trailmaking Test from the Halstead–Reitan Neuropsychological Battery.[29] A list of these procedures is presented in table 1.

Statistical analysis. Paired *t*-tests were used to investigate neuropathologic and mental status differences between subjects who met or did not meet neuropathologic guidelines for AD based on SP and NFT counts. Correlations were computed between the mental status scores and DP, NP, and NFT average counts for each region. Statistical analyses were completed using ABSTAT version 7.02 (Anderson Bell, Parker, CO), SAS version 6.12 (SAS Statistical Institute, Cary, NC), and SYSTAT version 7.0 (SPSS, Chicago, IL).

Results. The mean age of the 59 cases at autopsy was 83.9 years (SD 7.4, range 69 to 100) and these volunteers had completed an average of 16.3 years (SD 2.6) of education. Many of the cases in this initial sample had not completed more than one assessment before death. Therefore, only data from their last (before autopsy) mental status examination were used. Their last mental status examination occurred approximately 6 to 9 months before autopsy (mean time between assessment and autopsy 8.02 months, SD 5.16).

Neuropathologic findings. Regional pathology for cases classified using the NIA-RI guidelines is shown in figures 1 and 2 (to access Khachaturian and CERAD classification data, please visit our Web site at www.neurology.org and click on the title link for this article). Mean regional counts showed that SP were more prevalent in cortical regions than in medial temporal lobe structures. The opposite pattern was found for NFT, which were more prevalent in the hippocampus, entorhinal cortex, and amygdala. Comparisons between the normal and AD-like groups based on Khachaturian and CERAD criteria for AD showed an expected mean difference in SP for all cortical regions. However, group differences in NFT counts were

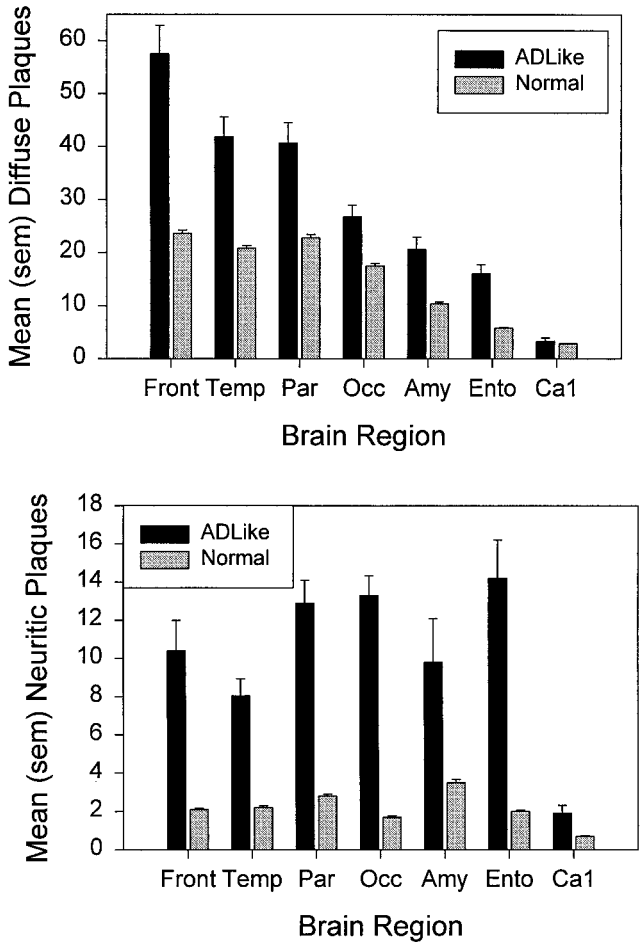

Figure 1. Mean (SEM) diffuse and neuritic senile plaque counts for intact older adults by brain region using National Institute on Aging–Reagan Institute neuropathologic classification.

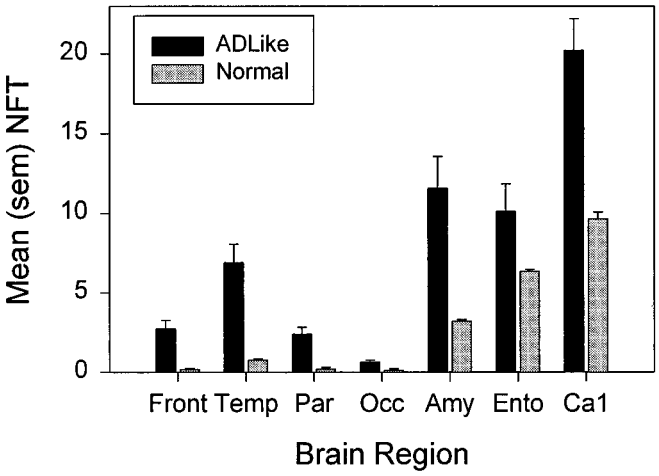

Figure 2. Mean (SEM) neurofibrillary tangle (NFT) counts for intact older adults by region using National Institute on Aging–Reagan Institute neuropathologic classification.

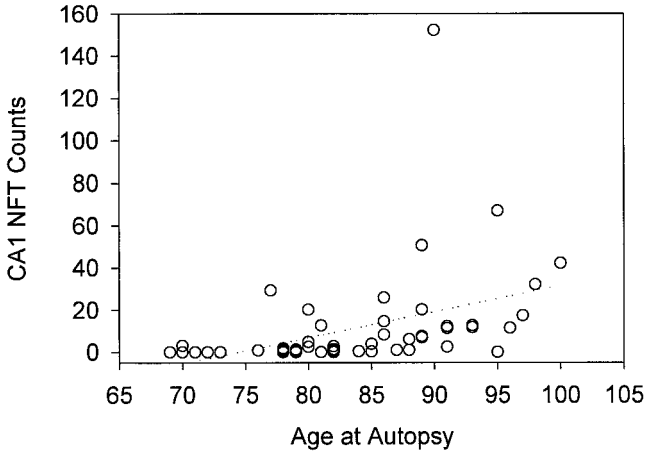

Figure 3. Scatterplot of age at autopsy and CA-1 neurofibrillary tangles (NFT).

not observed in the CA-1 region. When corrections were applied for multiple comparisons, most of the group differences in mean neocortical and hippocampal NFT counts were no longer significant.

Several regional changes in DP, NP, all SP, and NFT were associated with age at autopsy (table 2). However, with the exception of NFT in the CA-1 region (Bonferroni adjusted $r = 0.41$, $p < 0.05$; figure 3), correlations between autopsy age and neuropathologic markers were not reliable after correction for multiple comparisons.

DP were much more common than NP in these subjects in all regions. DP were most common in the amygdala, inferior parietal lobule, occipital lobe, middle frontal gyrus, and middle temporal gyrus. Comparisons between the normal and AD-like groups showed a greater number of DP and NP in the AD-like groups in all regions investigated. Even with correction for multiple comparisons, these differences remained robust with the exception of the CA-1 and occipital regions. Further, the correlations after adjustment for multiple comparisons between age at autopsy and DP and NP counts were not significant (see table 2).

Other associated neuropathologic findings are detailed in the following. Four subjects had Lewy bodies (a typographical error mistakenly showed five in a previous report).[25] Two subjects had more than five Lewy bodies in selected neocortical and allocortical regions and met the criteria for the pathologic diagnosis of dementia with Lewy bodies[30]; one subject had brainstem and neocortical Lewy bodies but did not meet these criteria. One other subject had brainstem Lewy bodies. None of the cases with Lewy bodies met NIA-RI criteria. Fourteen subjects had argyrophilic grains. Twenty-one subjects had gross or lacunar infarcts and 36 subjects had microscopic infarcts (not detected grossly). Two subjects exhibited hippocampal sclerosis.

Table 2 *Correlations between diffuse (DP), neuritic (NP), and all senile plaques (SP) plus neurofibrillary tangle (NFT) counts with age at autopsy*

Measure/region	DP	NP	SP	NFT
Middle frontal gyrus	0.28*	0.25*	0.30*	−0.01
Middle temporal gyrus	0.30*	0.25*	0.31*	0.11
Inferior parietal lobule	0.21	0.15	0.22	−0.04
Occipital (area 18)	0.29*	0.26*	0.32†	0.21
CA-1	0.22	0.36†	0.27*	0.41‡
Amygdala	0.19	0.22	0.23	0.39‡
Entorhinal	0.21	0.13	0.23	0.13

* $p \leq 0.05$, † $p \leq 0.01$, $p \leq 0.001$ before correction for multiple comparisons.

Mental status findings. No differences were found between the normal and AD-like groups in age at autopsy, age at mental status testing, or education. Differences in mental performance were not observed between the Khachaturian and CERAD neuropathologically classified AD-like groups on any of the cognitive measures (for more information, please visit our Web site at www.neurology .org and click on the title link for this article). When the NIA-RI guidelines were applied to these cases, differences were present only in performance on immediate paragraph recall and delayed recall of a word list in the AD-like group compared with the normal group. No differences were found for any other cognitive measures (table 3).

Because six of the seven participants who were classified as AD-like using the NIA-RI guidelines had repeated assessments of memory, an additional exploratory analysis was completed. Logical memory immediate recall and word-list delayed recall measures were investigated with a one-way repeated measures analysis of variance (ANOVA) with the factor of annual assessment (figure 4). No effect of assessment was found for logical memory (immediate recall). However, a main effect of assessment was found for the delayed verbal recall measure. Post hoc comparisons between means (Scheffé test) showed significant differences in delayed recall from baseline by the fourth assessment (roughly 3 years before autopsy).

Discussion. The neuropathologic findings in this group of older adults with prospective mental status examination parallel the data reported by others who have investigated AD changes in prospectively evaluated normal older adults. Most of these studies showed modest numbers of SP and NFT in nondemented elderly subjects and NFT were more common

Table 3 *Selected mean (SD) mental status scores by neuropathologic criteria**

		Khatchaturian		CERAD		NIA-RI		
Measure	All cases	AD-like	Normal	AD-like	Normal	AD-like	Normal	*t-test*
MMSE	27.97 (1.85)	27.72 (2.28)	28.20 (1.30)	27.47 (2.26)	28.14 (1.68)	28.00 (1.53)	27.96 (1.90)	NS
Memory								
Word List Learning (max 30)	18.56 (4.55)	18.73 (4.15)	18.41 (4.95)	18.77 (4.55)	18.50 (4.60)	16.83 (5.12)	18.78 (4.49)	NS
Delayed recall (max 10)	5.76 (2.33)	5.62 (2.08)	5.90 (2.57)	5.31 (2.14)	5.90 (2.40)	4.00 (2.37)	5.98 (2.26)	2.02†
Savings	77.6% (25.3)	77.7% (26.6)	77.4% (24.7)	75.8% (29.4)	78.1% (24.3)	60.8% (35.2)	79.6% (23.5)	NS
WMS logical	26.38 (7.56)	26.25 (5.35)	26.50 (9.26)	24.25 (4.94)	27.05 (8.16)	20.80 (4.21)	27.0 (7.62)	2.82†

* All *t*-tests for comparisons between Khatchaturian and Consortium to Establish a Registry for AD (CERAD) groups were nonsignificant; † $p < 0.05$.

NIA-RI = National Institute on Aging–Reagan Institute; MMSE = Mini-Mental State Examination; WMS = Wechsler Memory Scale.

in the hippocampus and entorhinal cortex. A previous study[20] found NFT present in the entorhinal cortex and hippocampus of most elderly individuals irrespective of their cognitive status and suggested that NFT are associated with advanced age and are not sufficient for the expression of dementia. Our study differed somewhat in that 14% of subjects had no NFT.

Most studies found SP to be mainly in the neocortical regions in nondemented elderly. Morris et al.[13] described neuropathologic findings in 21 longitudinally followed subjects, nine of whom had a high density of neocortical SP. Seven of these had CDR ratings of 0.5 and they suggested that SP may not be present in normal aging but represent presymptomatic or incipient AD. In our study, 69% of subjects had NP in at least one neocortical or allocortical section. Katzman et al.[19] described 10 prospectively evaluated subjects with preserved mental status with marked numbers of neocortical NP and few or no cortical NFT. They suggested that this group of patients had incipient AD. Kazee et al.[31] also described a subgroup of cognitively normal controls that had neocortical NP, whereas Haroutunian et al.[20] found small numbers of NP in the neocortex of 18 subjects with CDR scores of 0. There was a significant increase in neocortical NP density with increasing CDR scores and the authors suggest that NP are the earliest neuropathologic lesions in AD. Thus, although the overall findings in normal patients studied prospectively have some similarities, the interpretations differ somewhat. Despite these studies, the criteria for the recognition of incipient or presymptomatic dementia remain to be determined.

One of the main findings in our study is that 49.2% of subjects met Khachaturian criteria for AD, 25.4% met CERAD criteria, and 11.9% met at least intermediate likelihood of the NIA-RI guidelines. Subjects in this study were separated into those who had sufficient AD-like neuropathologic changes to meet these separate criteria and those who did not. Subjects meeting the Khachaturian and CERAD criteria for the neuropathologic diagnosis of AD, compared with those who do not, show no statistically significant difference in the broad series of mental status measures performed. Comparing these same measures in those cases who met the NIA-RI guidelines with those individuals who did not revealed a significant difference in only immediate paragraph recall and delayed word list recall in those with AD-like changes. The exact meaning of the decline in these memory measures in the NIA-RI AD-like group is not clear. Although we did not perform a CDR on our subjects, one possible interpretation is that these individuals (given the group differences in memory performance) could have been similar to the subjects with a CDR of 0.5 described by others[18,21] and thus might represent incipient or presymptomatic AD. Our study suggests that the NIA-RI guidelines may be more sensitive in detecting subtle early changes than the Khachaturian and CERAD criteria.

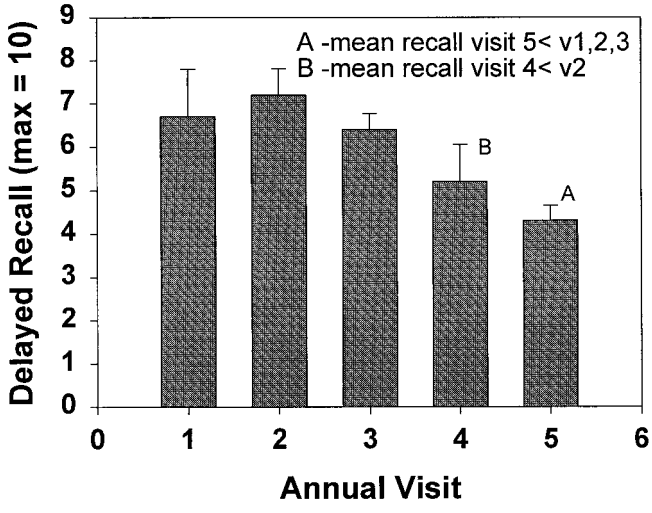

Figure 4. Mean (SD) differences in annual word-list delayed recall for six individuals followed longitudinally who met National Institute on Aging–Reagan Institute neuropathologic guidelines for AD.

The NIA-RI criteria place more emphasis on NFT than the two other criteria, which suggests that NFT may be more important in the incipient or presymptomatic stage of AD. Further, the presence of NFT appears to improve the specificity of the NIA-RI guidelines for the neuropathologic determination of a clinically diagnosed dementia, but a significant overlap between clinically demented and nondemented cases has recently been described in 47 cases evaluated with the NIA-RI classification scheme.[32] Patients with mild cognitive impairment (MCI), as described by Petersen et al.,[33] demonstrated differences from clinically normal elderly on similar memory measures. This suggests that the subjects in our NIA-RI AD-like group could possibly be classified as having MCI, even though they did not meet the cognitive criteria for MCI. Regardless of the interpretation, our data suggest that decreased verbal memory performance is associated with more advanced AD-like changes, especially in medial temporal lobe structures, which could be the substrate for MCI or presymptomatic AD.

One feature that stands out in this study is that in the group of subjects with AD-like changes, 61% had microinfarcts and tolerated all these changes without showing gross cognitive or functional decline. Underdiagnosis of preclinical AD is a possibility in our subjects who had significant neuropathologic changes in neocortical and medial temporal lobe structures for two reasons. First, because this is a highly educated group, use of mental status tests may be insensitive to early cognitive dysfunction associated with evolving AD. Second, these tests reflect a threshold of cognitive impairment that has not been reached by these AD-like subjects, possibly due to their cognitive reserve.[34,35] If this is the case, then those subjects in our population who have lower levels of educational attainment and are therefore at greater risk of AD (reviewed in Schofield and Mayeux[36]) may show greater associations between cognitive tests and neuropathologic classification. Although age-associated changes in memory may be the result of hippocampal NFT accumulation in normal aging, pathologic aging may reflect an accelerated rate of NFT and NP formation leading to dementia.[37-39] Finally, reports by Terry et al.[40] and Scheff et al.[41-43] show associations between synapse loss and mental functioning. Based on these reports, we are continuing to investigate these markers and their association with cognition in this unique group of older adults.

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