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Neuropathologic Alterations in Mild Cognitive Impairment: A Review

William R. Markesbery, M.D.
Departments of Pathology and Laboratory Medicine, and Neurology; Sanders-Brown Center on Aging, and Alzheimer's Disease Center, University of Kentucky College of Medicine

Abstract

Mild cognitive impairment (MCI), the earliest clinically detectable phase of the trajectory toward dementia and Alzheimer's disease (AD), catalyzed the desire for even earlier detection and prevention of AD. Although it is a clinical diagnosis, its underlying neuropathological findings are just being defined. MCI is best studied in longitudinally followed patients in centers that are experienced in dementing disorders. In this review of the few major clinical-pathological reports of longitudinally followed patients, it appears that most autopsied amnestic MCI (aMCI) patients are on a pathway toward AD. Neurofibrillary pathology in entorhinal cortex, hippocampus, and amygdala – not amyloid plaques – is the major substrate for aMCI and for memory decline. In addition, many MCI patients have other concomitant pathological alterations, the most common of which are strokes, but also include argyrophilic grains and Lewy bodies. These findings are not surprising because most MCI autopsied cases have been in the older (80 to 90 year) range where these findings are common. In early AD, the phase following MCI, the significant change is an increase in neurofibrillary tangles in the neocortex that correlates with an increase in Braak score and the observed clinical progression.

Keywords

Alzheimer's disease; mild cognitive impairment; neurofibrillary tangles; preclinical Alzheimer's disease

INTRODUCTION

The major neuropathological findings of Alzheimer's disease (AD) – neurofibrillary tangles (NFT) and senile plaques (SP) – have been known for many years. However, it was left for Roth et al. [1] and Tomlinson et al. [2] in two seminal publications to describe that the changes of AD were the most common neuropathologic substrate for the disease and not cerebral ischemia or diminished blood flow to the brain. In subsequent years, the diagnosis of AD was best made through the time- honored exercise of clinical-pathological correlation. A definite diagnosis of advanced AD was determined by a gradual decline in cognitive function by history and the presence of abundant NFT and SP in the neocortex and medial temporal lobe structures. [3,4] This is still the most precise way of making a diagnosis of AD.

In addition to NFT and SP, the neuropathologic findings in AD include neuropil threads, specific neuron loss, and synapse loss. NFT are composed of paired helical filaments and straight filaments containing hyperphosphorylated tau. Neuropil threads, primarily in

University of Kentucky, 101 Sanders-Brown Building, 800 S. Limestone Street, exington, KY 40536-0230, Telephone: (859)323-6040, Fax: (859)323-2866, Email: wmark0@email.uky.edu

dendrites, are also composed of paired helical filaments with abnormally phosphorylated tau. Braak and Braak [5] showed that neurofibrillary pathology follows a predictable progressive pattern which they placed into six stages (I–VI). The NFT start in the transentorhinal area (I) and spread into the entorhinal cortex and hippocampus (II). In stages III and IV, the neurofibrillary pathology increases in the entorhinal cortex, hippocampus, adjacent inferior temporal cortex, and amygdala. Stages V and VI are characterized by spread to the neocortical association cortex and other brain regions.

Senile plaques, composed of focal extracellular deposits of amyloid beta peptide, have diverse morphological forms and names: neuritic plaques (NP) or classic plaques; diffuse plaques (DP); primitive plaques; burned out plaques; cotton-wool plaques; fleecy or lake-like deposits. However for practical purposes they are best referred to as neuritic, those containing neurites; and diffuse, those without neurites. Thal et al. [6] hypothesized that amyloid deposition in the brain occurs in stepwise phases. In phase 1–3 in nondemented older individuals, amyloid deposits appear first in the neocortex and subsequently in allocortex, diencephalon, and basal ganglia. In AD the above regions are involved in addition to midbrain and lower brainstem (phase 4) and cerebellum (phase 5).

The neuropathologic diagnostic criteria for AD have undergone many changes over 20 years. In 1985 a group of neuropathologists developed the first criteria known as the Khachaturian criteria [7], which were based on the density of SP (NP and DP) in the neocortex in relation to age and presence of dementia. In individuals under fifty years old, counts exceeding 2–5/mm^2 field in neocortex were considered diagnostic of AD. Patients between 50 to 65 years old with greater than 8/mm^2, those between 65–75 years old with greater than 10/mm^2, and those over age 75 with greater than 15/mm^2 were thought to have AD. These criteria did not include NFT and did not differentiate NP from DP.

The Consortium to Establish a Registry for Alzheimer's disease (CERAD) criteria developed in 1991 [8] are based on the semiquantitation (sparse, moderate, frequent) of NP in frontal, temporal, and parietal lobes. The highest value of NP is compared with the ages of patients to yield an age-related plaque score of a) uncertain evidence of AD, b) suggestive of AD, or c) indicative of AD. This score is integrated with the clinical history to arrive at a diagnosis of "possible, probable, or definite" AD.

The National Institute on Aging and Reagan Institute (NIA-RI) criteria, developed in 1997 [9], use the CERAD plaque score and the Braak and Braak score to reach a likelihood of the diagnosis of AD. The likelihood of AD is "low" with CERAD sparse and Braak stage I-II, "intermediate" with CERAD moderate and Braak III-IV, and "high" with CERAD frequent and Braak V–VI. Problems occasionally arise when the scores are incongruent and do not fit the NIA-RI classification precisely. While none of the criteria are ideal, the NIA-RI criteria are the best we have to use at present and their use is mandated for all NIA-funded Alzheimer's Disease Centers.

In the present era, the major goal of research in AD is prevention of the disease, which entails early detection before the onset of symptoms. Recently the concept of mild cognitive impairment (MCI), the earliest clinically detectable phase of dementia and AD, has gained importance in early detection. MCI is a clinical diagnosis and neuropathologic findings are just beginning to be defined. No specific neuropathologic criteria have been established for MCI. In addition, attempts to detect the disease before onset of symptoms, termed preclinical AD (PCAD), through genetic markers, imaging, neuropsychological measures and biomarkers, have kindled hope for early detection.

MILD COGNITIVE IMPAIRMENT

The details of the clinical evaluation and subtyping of MCI have been thoroughly reviewed by others in this special series of articles. Most investigators use the criteria described by Petersen [10] for amnestic MCI (aMCI): a) memory complaints, preferably corroborated by an informant; b) objective evidence of memory impairment for age and education; c) intact general cognitive function; d) no or minimal changes in activities of daily living (ADLs); and e) not demented. Other forms of MCI include multiple domain and single non-memory domain types. The neuropathologic features of aMCI have been described more than those for nonamnestic MCI because the latter are less frequent [10] and fewer autopsies are available. MCI is best studied in longitudinally followed patients who have been evaluated at least annually and have been evaluated as near death as possible. This review primarily concentrates on the major clinical-pathological reports of longitudinally followed cohorts. There are only a few neuropathological studies of MCI from longitudinally studied cohorts [11–18] and they show some common features (Table). MCI is a clinical diagnosis and different evaluation processes and criteria are used for its diagnosis; thus, what may be MCI in one clinic or center might not be in another. The rate of progression from normal aging to MCI to dementia varies considerably and not all MCI patients progress to dementia [19]. Although the objective criteria are clear, determining that a person dies in the MCI phase of the dementing process can be difficult in some cases because intercurrent medical illnesses or use of potent medications in the elderly can interfere with cognition. These factors must be clearly evaluated and considered in the diagnosis.

In 1999, Price and Morris [12] studied 15 longitudinally followed patients with Clinical Dementia Rating (CDR) Scale scores of 0.5 and found all patients had neuropathologic changes of AD at autopsy. In another report from Washington University's Alzheimer's Disease Research Center [17], they found that in 6 subjects with CDR scores of 0.5 with uncertain dementia at entry into this study, all had neuropathological AD at autopsy. In another group of 7 with CDRs of 0.5 and a diagnosis of incipient AD, and another group of 11 with CDRs of 0.5 and a diagnosis of AD at entry, all had neuropathological features of AD at autopsy later in life (except that 1 had frontal dementia and 2 had vascular dementia.) They suggested that most all MCI patients had AD.

A report from the Religious Order Study of 37 longitudinally followed MCI subjects compared to 60 without cognitive decline and 83 demented subjects showed that MCI patients had intermediate AD pathology between normal and demented subjects [16]. For MCI criteria they used subjects rated as cognitively impaired by the neuropsychologist but not demented by the examining physician. Persons with MCI also had intermediate levels of cerebral infarction between normal and demented subjects and 3 had Lewy bodies. The dementia group contained patients with AD, cerebral infarction, Parkinson's disease, dementia with Lewy bodies, and combinations of these conditions making it difficult to compare to other MCI studies. They used a global AD pathology score and in MCI patients the score was approximately 50% higher than in normal controls and about 60% of those with dementia. More than half of MCI patients had Braak stages of III/IV and more than half met CERAD AD probable or definite AD. Four MCI patients were high likelihood, 19 were intermediate likelihood, and 14 were low likelihood for AD by NIA-RI guidelines. The mean Braak score was 3.57 in MCI suggesting that the bulk of the neurofibrillary pathology was in the medial temporal lobe structures. About a third of persons with MCI had one or more cerebral infarctions. Their studies suggested MCI is related to AD pathology and cerebral infarction.

Mitchell et al [13] studied NFT and neuropil threads (using tau immunohistochemistry and quantitative image analysis) in entorhinal and perirhinal cortices in 14 normal controls, 9 MCI, and 8 AD patients from the Religious Order Study. They found NFT and neuropil threads were

significantly lower in persons without cognitive impairment compared to those with MCI or AD. NFT, but not neuropil threads, significantly correlated with episodic memory decline.

In a study of autopsied nuns, Riley et al [14] used a complex system to classify subjects into two large groups: one group included subjects with normal memory that were either intact, had mild impairments, or had global impairment. The other group had memory decline and either mild impairment, global impairment, or were demented. Their mild impairment groups included some MCIs with multiple domain and nonmemory domain types. Most of their mild impairment groups fell within Braak scores of I–IV. They concluded that neurofibrillary pathology is one of the major substrates in MCI.

Our study used 10 aMCI patients compared with 10 early AD (EAD) patients and 23 normal controls [15]. All were followed longitudinally as part of our normal aging study and were evaluated annually as described previously [20]. The mean ages were 89 years (aMCI), 87 years (EAD), and 82 years (controls). The criteria of Petersen et al [10] and CDR scores from 0 to 0.5 were used for the diagnosis of MCI by consensus conference. EAD was defined as decline in cognitive function from a previous level of impairment in one or more areas of cognition in addition to memory, altered ADLs, CDR scores of 0.5 to 1, and a clinical evaluation to exclude other causes of dementia. All controls were free of cognitive symptoms and had normal cognitive test scores, ADLs, and neurologic exams. Controls had Braak scores of I or II. All subjects had NFT, NP, and DP quantified in the 5 most involved fields of the middle frontal gyrus, middle temporal gyrus, inferior parietal lobule, posterior cingulate gyrus, hippocampal CA1, subiculum, entorhinal cortex, and amygdala. The modified Bielschowsky stain and the Gallyas stain were used for the direct counting of NFT, NP, and DP.

Patients with aMCI had no significant differences in DP in all neocortical or medial temporal lobe structures compared to normal controls. Significantly increased NP were present in all neocortical regions and amygdala in aMCI compared to controls. NFT were significantly increased in the amygdala, entorhinal cortex, CA1, subiculum and inferior parietal lobule in aMCI compared to normal controls.

No significant differences were found in DP between MCI and EAD except for an increase in middle temporal gyrus in EAD. Patients with EAD compared to aMCI showed no significant increase in NP in neocortex; however, NP were increased in amygdala and subiculum in EAD. NFT were significantly increased in middle frontal gyrus, middle temporal gyrus, amygdala, and subiculum in EAD compared to aMCI. The AD pathology was much greater in MCI than in controls but was intermediate between controls and EAD. One aMCI patient had a lacunar infarct in the caudate nucleus and four patients had one or more microinfarcts. Three aMCI patients had mild to moderate argyrophilic grains formation and one had Lewy bodies in the amygdala. Thus, the major difference between aMCI and EAD was a significant increase in NFT in the neocortex that correlated with an increase in Braak stage scores. In addition, our study showed delayed memory performance correlated with NFTs in CA1 and the entorhinal cortex.

Other reports comparing aMCI to longitudinally followed, precisely diagnosed EAD patients have not appeared in the literature. Like aMCI, all EAD patients were diagnosed premortem and died a mean of 9.3 months after the last evaluation. They lived a mean of 5.4 years between their clinical diagnosis and death compared to a mean of 2.6 years for aMCI. We believed that our EAD patients were in the phase of the disease just beyond aMCI. All were Braak stage V except one (mean of 4.8). As noted above, NFTs were increased in the neocortex, amygdala, and subiculum in EAD compared to aMCI. This neuropathologic progression of NFTs into the neocortex in the transition from aMCI to EAD is in keeping with the changes described by

Braak and Braak [5] and with the observed clinical progression. It also underscores the importance of NFT in progression of the disease.

Since our initial report in 2006 of 10 aMCI patients, we have completed autopsies on six more patients (four women and two men) with the premortem clinical diagnosis of aMCI (Markesbery – unpublished data). The mean age was 90.3 years. Using CERAD criteria, four subjects were rated as moderate, one frequent, and one had no amyloid deposits (96 years old). The Braak scores ranged from II to V with a mean of 3.5. Four met NIA-RI criteria for intermediate likelihood, one for low likelihood, and one could not be given an NIA-RI score because of the absence of amyloid plaques but had a Braak score of IV. Three had no chronic infarcts, one had a cerebellar microinfarct, and another had an amygdala microinfarct. One had several neocortical microinfarcts. As in our initial 10 cases, the predominant change was the presence of neurofibrillary pathology in medial temporal lobe structures and modest neocortical NP.

Petersen et al. [18] reported the neuropathologic findings in 15 longitudinally followed subjects from a community-based study that died while their clinical diagnosis was aMCI. They were compared with 28 normal controls (CDR 0) and 23 patients with the clinical diagnosis of probable AD. They found a broad heterogeneous spectrum of neuropathological findings in aMCI including the presence of hippocampal sclerosis (3), argyrophilic grains (7), infarcts (4), Lewy bodies (1), early AD (2), and one with no abnormal findings (Braak score 0, no SP). Of their patients, one met NIA-RI high likelihood criteria, three met intermediate, eleven had low likelihood, and one was no probability. The mean Braak score was 2.9. The most common finding was neurofibrillary pathology in medial temporal lobe structures. They concluded that the neuropathological findings of aMCI seemed to be intermediate between controls and very early AD. Their aMCI patients had slightly less AD pathology and more heterogeneous pathology than our group of aMCI subjects.

Jicha et al [11] described followup of 34 patients from a community-based cohort with MCI who progressed to dementia and eventually underwent postmortem brain analysis. The final neuropathologic diagnoses were 24 AD (18 of 24 with aMCI and 6 with multiple-domain MCI), 3 Lewy body dementia, 2 hippocampal sclerosis, 2 nonspecific tauopathies, 1 argyrophilic grains dementia, 1 progressive supranuclear palsy, and 1 frontotemporal dementia. Other concomitant pathologies included cerebrovascular disease in 35%, argyrophilic grains in 53%, and Lewy bodies in 26%. This study points out the heterogeneous pathological outcome of MCI following progression to dementia. All cases had sufficient pathological alterations in medial temporal lobe structures to account for the amnestic decline.

Two reports of four longitudinally followed MCI patients compared to seven normal controls revealed that those with MCI had significantly increased NFT in the nucleus basalis of Meynert [21] and locus ceruleus [22], indicating that alterations in these structures were an early event in the aging-MCI-AD continuum.

Scheff et al [23,24] showed that synapse numbers were decreased in the stratum radiation of hippocampal CA1 and the outer molecular layer of the dentate gyrus in aMCI longitudinally followed patients compared to normal controls but did not reach statistical significance. Synaptic reduction was 13% in the outer molecular layer and 18% in stratum radiation in MCI compared to controls. However, comparing MCI to mild AD, using NINCDS-ADRDA criteria [3], synapse number was significantly decreased (44% in the outer molecular layer and 55% in stratum radiation) in both areas in mild AD, suggesting that MCI was a transition stage between normal controls and mild AD.

As an example of a study of MCI in patients that were not longitudinally followed, Saito and Murayama [25] evaluated 545 serial autopsy cases from the Brain Bank for Aging Research

in a general geriatric hospital in Tokyo. These cases represented a population with a mean age of 80.7 years. They studied 57 cases with a CDR rating of 0.5, which was determined retrospectively through chart review or interview with the patient's physicians or caregivers. The neuropathological diagnoses were: 33 with neurodegenerative pathology, 9 with vascular pathology, 4 with combined neurodegenerative pathology and vascular pathology, 2 with hippocampal sclerosis, 2 with cerebral contusion, one with metabolic disease, and 6 with no pathological changes. Of the neurodegenerative group, 31% had AD changes, 25% had neurofibrillary tangle predominant changes, 36% had argyrophilic grains, and 18% had dementia with Lewy body changes. Six cases had nonspecific pathology. These authors concluded that the pathology in those with CDRs of 0.5 (MCI) is characterized by multiple pathological backgrounds. This study is difficult to put into context of other MCI studies because they did not use longitudinally followed patients and they used a retrospective CDR.

It is noteworthy that most of the studies described above were on elderly individuals with mean ages of 80 years plus. This suggests that MCI is found more frequently in the 80+ age group or that younger individuals with MCI do not frequently come to autopsy.

Thus, the above studies of predominantly aMCI patients have shown a spectrum of pathological changes but the most consistent changes are those of AD. Neurofibrillary pathology dominates the AD changes, which are most prominent in the medial temporal lobe structures and most are in the Braak stage III–IV range. The next most common change is cerebral infarctions. Argyrophilic grains and the presence of Lewy bodies make up a few of the cases.

MCI COMPARED TO NORMAL AGING

Attempting to compare MCI to normal control patients presents some difficulties. While some studies such as ours used individuals with 0-II Braak stage, others used Braak III to IV stages. As pointed out by Morris [26], exclusion of the full spectrum of variability in neurofibrillary pathology in normal aging possibly increases the discriminatory power of NFT and NP density to differentiate MCI from normal aged brains. Our intent was to have controls that were normal cognitively and neuropathologically. Using the full spectrum of AD pathology in normal aging raises the question of whether those with abundant AD pathology and normal antemortem cognition are truly normal or have PCAD.

PCAD, a product of retrospective studies, is more of a concept than a proven disease entity. It is characterized by cognitively normal individuals with normal ADLs and no neurologic deficits who at autopsy show an abundance of neurofibrillary pathology and amyloid plaque deposition. The neuropathologic changes are the key features in the diagnosis of PCAD but no criteria have been proposed for this entity. In general, these individuals usually have sufficient neuropathology in the medial temporal lobe structures to meet a Braak grade III or greater. They also have sufficient neocortical NP to meet CERAD moderate or frequent criteria. Also most have considerable DP formation to meet the outmoded Khachaturian criteria for the diagnosis of AD. Many meet the NIA-RI criteria for intermediate likelihood and a few meet the high likelihood criteria for the neuropathologic diagnosis of AD.

The relationship between PCAD and MCI is not known. Whether these individuals would have progressed to develop MCI and AD had they lived longer or whether they would have remained cognitively normal perhaps due to greater brain reserve is not known. However, it seems logical that if the AD burden continued to increase and, if it is important in the disease, a threshold would have been reached and cognitive symptoms would have developed.

Our early study of 59 cognitively normal, elderly adults showed that 49% met Khachaturian criteria for AD, 26% met CERAD probable or definite criteria, and 12% met intermediate likelihood or high likelihood NIA-RI guidelines for the neuropathologic diagnosis of AD

[27]. Bennett et al [28] reported that, of 134 persons without cognitive impairment from the Religious Order Study and Rush Memory and Aging Project, at autopsy 2 met NIA-RI high likelihood criteria, 48 met intermediate likelihood criteria, and 79 met low likelihood criteria; 29 had cerebral infarctions; and 18 had Lewy bodies. They concluded that AD pathology can be found in brains of older persons without dementia or MCI and that the pathology related to subtle changes in episodic memory.

Erten-Lyons et al [29] described autopsy findings from 36 longitudinally followed subjects with Braak stage V or VI and moderate or frequent NP scores based on CERAD standards. Twelve subjects had normal cognitive function and 24 had AD clinically. Seven of the normal subjects had Braak V scores and 6 had CERAD frequent NP scores. Two had large vessel strokes and two had smaller infarcts. None had Lewy body pathology. In multiple regressive analyses, hippocampal volume and total brain volume (on antemortem MRI studies) were significantly larger in the normal control group. These findings support greater brain reserve or other protective mechanisms such as intact synapses or genetic resistance to apoptosis of neurons in PCAD subjects.

In my experience of studying neuropathology of the elderly brain, my observation is that none of our PCAD cases have the severe advanced or end-stage neuropathologic features of AD [30] characterized by severe atrophy, extremely large numbers of NFT, NP, and neuropil threads seen in long surviving cases. By the same token, reviewing PCAD cases in a blinded manner does not allow one to differentiate them from MCI or EAD on a purely neuropathologic basis. Said another way, it is not possible to define a maximum neuropathological threshold for clinical AD using Khachaturian, CERAD, or NIA-RI criteria.

Recent publications have suggested that subtle changes in neuropsychological testing and imaging can detect those with PCAD that will progress to MCI or AD (reviewed in [31]). Galvin et al [32] showed that increased age, depressive features, slow psychomotor performance, and absence of the practice effect on neuropsychological testing were predictors of PCAD. General measures of cerebral atrophy and entorhinal and hippocampal volumes are used in predicting conversion from normal to MCI [33–35]. Smith et al [36] showed that medial temporal and left parietal gray matter volumes in normal subjects predicted MCI within 5 years with 76% accuracy, which was further enhanced to 87% by combining gray matter volume with raw Wechsler memory scores. Diminished PET resting glucose metabolism in the posterior cingulate gyrus and parietal region has been observed in asymptomatic subjects at high risk with one *APOE* ε-4 allele and a positive family history of AD [37]. PET-based amyloid imaging holds some promise for predicting PCAD [38] but has the same problem as neuropathology in determining a minimum threshold for detecting clinical AD.

SUMMARY

MCI is a difficult diagnosis and its outcome in every case is not precisely certain. It is best studied in longitudinally followed patients in centers experienced with dementing disorders. In these reports, 70% to 100% of MCI patients autopsied have findings that suggest they are on a pathway toward AD. It appears that neurofibrillary pathology in medial temporal lobe structures is the major substrate for MCI and for memory decline – not amyloid plaques. The MCI studies to date have been on older Caucasian individuals and, as in AD, many MCI subjects have other concomitant pathological alterations, the most common of which is cerebrovascular disease. Also, because we are dealing with an older population of patients, difficulties in interpretations occur because some normal elderly have advanced AD brain pathology. As pointed out by Bennett et al. [16], caution should be exercised in using MCI patients in clinical trials because many already have disease pathology.

Detecting those at risk many years before symptoms occur is one of the most critical problems in AD. Understanding the neuropathology of the earliest phase of AD leads to a better overall concept of the disease, but detection of this phase by imaging or any other method is probably too late because the pathology is well established in most patients. What is needed is a consistent biomarker in blood or CSF or genetic markers that will detect the disease before it reaches a threshold to show clinical symptoms. Although we do not have preventive agents at present that will eventually be achieved.

Abbreviations

AD	Alzheimer's disease
aMCI	amnestic mild cognitive impairment
CDR	Clinical Dementia Rating Scale
DP	diffuse plaques
EAD	early Alzheimer's disease
MCI	mild cognitive impairment
NP	neuritic plaques
NFT	neurofibrillary tangles
PCAD	preclinical Alzheimer's disease
SP	senile plaques

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Table

Clinical-pathological reports of longitudinally followed subjects with MCI

	Criteria used for MCI diagnosis	Number of MCI subjects	Source of Subjects	Pathology	Braak score
Price & Morris, 1999 [12]	CDR 0.5	15	Washington University ADRC Community-based population	Increased NFT, DP and NP neocortex	N/A
Morris et al. 2001 [17]	CDR 0.5	24	Washington University ADRC Community-based population	21 out of 24 had AD	N/A
Mitchell et al. 2002 [13]	Other	9	Rush University ADC Catholic clergy	NFT in medial temporal lobe but not neuropil threads	N/A
Riley et al. 2002 [14]	Other	17	University of Kentucky Nun Study	NFT prominent	N/A
Bennett et al. 2005 [16]	Other	37	Rush University ADC Catholic clergy	AD pathology and cerebral infarction	mean 3.6
Markesbery et al. 2006 [15]	Petersen et al. CDR 0.5	10	University of Kentucky ADC Community-based population	Predominant NFT in medial temporal lobe structures; modest neocortical NP	mean 3.3
Markesbery unpublished data	Petersen et al CDR 0.5	6	University of Kentucky ADC Community-based population	Predominant NFT in medial temporal lobe structures; modest neocortical NP	mean 3.5
Petersen et al. 2006 [18]	Petersen et al	15	Mayo Clinic ADRC Community-based population	Predominant NFT in medial temporal lobe structures; other heterogeneous pathology	mean 2.9
Jicha et al. 2006 [11]	Petersen et al	34	Mayo Clinic ADRC Community-based population	24 out of 34 had AD	mean 4.1

[reference number]

Abbreviations: AD, Alzheimer's disease; ADC, Alzheimer's Disease Center; ADRC, Alzheimer's Disease Research Center; DP, diffuse plaques; CDR. Clinical Dementia Rating Scale; MCI, mild cognitive impairment; NFT, neurofibrillary tangles; NP, neuritic plaques