Neuropathologic Features of Amnestic Mild Cognitive Impairment

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Background: The neuropathologic substrate of amnestic mild cognitive impairment (aMCI) is not known.

Objective: To determine the neuropathologic features of patients who died while their clinical classification was aMCI.

Design: Cohort study.

Setting: Community based.

Participants: Sixty-six individuals, including 15 who had memory impairment beyond that allowed for aging but who were not demented, were studied along with 28 clinically healthy individuals and 23 patients with probable Alzheimer disease (AD) for comparison.

Main Outcome Measures: Standard neuropathologic techniques and classification according to Khachaturian, Consortium to Establish a Registry for Alzheimer Disease, and National Institute on Aging–Reagan criteria were used to analyze autopsy tissue from 15 individuals who died while their clinical diagnosis was aMCI. For comparison, autopsy data on age-matched groups of clinically healthy individuals and patients with probable AD were analyzed.

Results: Most patients with aMCI did not meet the neuropathologic criteria for AD, but their pathologic findings suggest a transitional state of evolving AD. All the patients with aMCI had pathologic findings involving medial temporal lobe structures, likely accounting for their memory impairment. In addition, there were many concomitant pathologic abnormalities, including argyrophilic grain disease, hippocampal sclerosis, and vascular lesions.

Conclusions: The neuropathologic features of aMCI matched the clinical features and seemed to be intermediate between the neurofibrillary changes of aging and the pathologic features of very early AD.

Arch Neurol. 2006;63:665-672

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The field of aging and dementia is moving toward earlier identification of incipient disease states. The concept of mild cognitive impairment (MCI) has evolved in recent years to represent the clinical transition between the cognitive changes found in normal aging and those of early Alzheimer disease (AD). Several international clinical trials evaluating a variety of interventions for MCI have recently concluded. The American Academy of Neurology has endorsed the concept of MCI with an evidence-based medicine practice parameter paper highlighting the importance of MCI as a clinical entity.

There is debate in the field regarding the specific clinical criteria, longitudinal outcome, and underlying neuropathologic features of MCI. It has been recognized that the concept of MCI may be heterogeneous, and although the most common subtype, that is, amnestic MCI (aMCI), presents with prominent memory impairment and likely progresses to AD, other subtypes, with different clinical criteria, have been proposed. One challenge in studying the transition between normal aging and AD is the paucity of pathologic material on patients with MCI. There are a few studies in the literature on the neuropathologic features of patients who are clinically mild and very few on patients who died while their clinical diagnosis was MCI.

For editorial comment see page 645

The present study draws on a longitudinal, community-based study of aging and dementia. Some members of this cohort have been followed for up to 18 years. Between September 1, 1986, and December 31, 2004, 15 patients died and underwent autopsy while their clinical classification was still aMCI. As such, this is one of the first studies to characterize the neuropathologic substrate of patients still in the clinical state of aMCI.
CLINICAL EVALUATION

During the past 18 years we followed more than 270 people who have received the diagnosis of MCI at some point in their clinical course. All were participants in the National Institute on Aging (NIA)–supported Mayo Clinic Alzheimer Disease Patient Registry.19 Participants were recruited prospectively in this project from primary care practices of the Division of Community Internal Medicine of the Mayo Clinic in Rochester. The medical records of individuals 65 years and older who had received a general medical examination were evaluated for any suggestion of a cognitive concern raised by the patient, a family member, or the examining physician. If a concern was raised about cognitive function, permission was requested to approach the patient for evaluation. Patients then underwent neurologic evaluation and neuropsychologic testing, neuroimaging, and laboratory studies. These studies have been approved by the Mayo institutional review board.

Patients were diagnosed as having aMCI if they fulfilled the following criteria: (1) memory concerns, usually by the patient, preferably corroborated by an informant, (2) objective memory impairment for age, (3) essentially normal general cognitive function as judged by the physician, (4) normal activities of daily living as judged by the physician, and (5) not demented. The diagnosis was made on a clinical basis; that is, a consensus committee comprising neurologists, a geriatrician, neuropsychologists, nurses, and other study personnel adjudicated each case. Specific neuropsychologic cutoff scores were not used; instead, the patients were diagnosed as having aMCI if their memory performance was impaired out of proportion to their other cognitive domains.5,10 These individuals may have had isolated memory impairments (single-domain aMCI) or may have mild impairments in nonmemory domains (multiple-domain aMCI). Their activities of daily living were essentially intact except for some of the minor impairments related to the memory disorder as documented by the Record of Independent Living and the Clinical Procedures for Recruitment, Evaluation, and Postmortem Evaluation of the Mayo Clinic Alzheimer Disease Patient Registry.18 Participants were recruited prospectively in this project from primary care practices of the Division of Community Internal Medicine of the Mayo Clinic in Rochester. These groups are described for the purpose of comparison from a research group using the same procedures for recruitment, evaluation, and postmortem evaluation as used for the patients with aMCI.

After initial assessment and enrollment, patients were reevaluated annually. At each reevaluation they were assessed clinically, and their performance was reviewed at the consensus conference. The consensus conference committee determined whether the patient continued to fulfill the criteria for MCI, had reverted to normal, had progressed to clinically probable AD, or had developed another form of dementia. We used the Diagnostic and Statistical Manual of Mental Disorders, Third Edition,24 for the diagnosis of dementia and the National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association22 criteria for AD. The clinical evaluation of the patients with MCI has been discussed in detail elsewhere.6

For comparison, we also describe 28 individuals who were clinically healthy at the time of death (Clinical Dementia Rating of 0) and were age-matched at death to the patients with MCI.23 We also describe a group of 23 age-matched patients with clinically probable AD who had undergone autopsy. Both groups had been enrolled in and had undergone the same investigations using the same procedures as the patients with aMCI in the Mayo Alzheimer Disease Patient Registry/Alzheimer Disease Research Center. These groups are described for the purpose of comparison from a research group using the same procedures for recruitment, evaluation, and postmortem evaluation as used for the patients with aMCI.

NEUROPATHOLOGIC ASSESSMENT

Regions in which the counting was performed were selected macroscopically, according to the method of Duyckaerts et al,26 as the areas of the slide where the cortical ribbon was the thinnest (ie, where the angle of section was the closest to 90° relative to the cortical pial surface). Quantitative pathologic findings were recorded, according to the method of Dickson et al,27 from ×200 microscopic fields, excluding fields at the crest of the gyri or the depth of the sulci. Ten contiguous fields were examined for all slides, except in the case of the amygdala, hippocampus, and entorhinal cortex, where pathologic findings from 5 contiguous fields were recorded. In an attempt to limit the possible variability in staining techniques and in researcher interpretation, plaques were defined as diffuse (DP), cored without dystrophic neurites (CP), and neuritic (NP). Difuse plaques were identified as deposits of finely granular material in the neuropil, sometimes with a more dense central core. Cored plaques lacked dystrophic neurites by silver staining or tau immunostaining but had distinct amyloid cores. Neuritic plaques were identified by the presence of dystrophic neurites, arranged radially to form a discrete spherical lesion averaging approximately 30 µm in diameter. Using a combination of silver, anti-amyloid– and anti-tau–stained sections, plaque subtypes were separated and counted. Neurofibrillary tangles (NFTs) were counted on Bielschowsky- and anti-tau–stained sections. All the results were normalized and expressed as number

AUTOPSY PROCEDURE

The brains were processed according to the protocol of the Mayo Alzheimer Disease Research Center Neuropathology Core. After external examination of the fresh specimen, the brain was divided by a sagittal cut into the right and left hemispheres. One hemisphere (usually the right) was serially sectioned into 1-cm coronal slabs, and alternate slices were frozen and fixed in paraformaldehyde; the other hemisphere (usually the left) was fixed for 7 to 10 days in 10% to 15% buffered formalin and was coronally sectioned into 1-cm slabs and examined. The neuropathologic protocol was performed according to the recommendations of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD)24 and the consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies.25 The following brain areas were routinely sampled: superior/middle frontal gyri (plane just anterior to the temporal tip), superior/middle temporal gyri (plane of the mammillary body), inferior parietal lobule (plane 1 cm behind the posterior pole of the splenium), calcarine (primary visual) cortex, anterior cingulate (plane of the anterior commissure), hippocampus with adjacent inferior temporal cortex (level of the lateral geniculate body), amygdala and entorhinal cortex (level of the mammillary bodies), nucleus basalis, basal ganglia, cerebellum, thalamus with subthalamic nucleus, midbrain (with substantia nigra), pons (with locus ceruleus), and cerebellum, as well as representative sections of any lesions noted grossly.

After routine processing in paraffin and cutting, sections were stained with hematoxylin–eosin, and selected sections were stained with modified Bielschowsky, Luxol fast blue/periodic acid–Schiff, and thioflav-S and immunostained for β-amyloid (clone 6F/3D) (Novocastra Laboratories Ltd, Newcastle upon Tyne, England), phosphorylated tau (clone AT8) (Eng-dogen, Woburn, Mass), α-synuclein (clone LB509) (Zymed Laboratories, San Francisco, Calif), ubiquitin (polyclonal) (Dako, Glostrup, Denmark), neurofilament protein (clone 2F11) (Dako), α-β-crystallin (polyclonal) (Chemicon International Inc, Temecula, Calif), and glial fibrillary acidic protein (polyclonal) (Dako).

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ber per square millimeter. Semiquantitative NP counts were performed according to CERAD guidelines24,28, to ensure uniformity in estimates between evaluators, the following guidelines were applied: sparse NPs consisted of 1 to 5 NPs/100 mm²; frequent NPs, 20 or more NPs/100 mm² (grade 1); moderate NPs, 6 to 19 NPs/100 mm² (grade 2); and rare NPs, 5 to 19 NPs/100 mm² (grade 3). Neuropathologic staging of NFT distribution was performed according to Braak and Braak.29 The presence of Lewy bodies in the substantia nigra, locus ceruleus, amygdala, cingulate cortex, and neocortex was noted using hematoxylin-eosin, α-synuclein, and ubiquitin immunostaining. Hematoxylin-eosin–stained sections were used for the assessment of infarcts and arteriolar disease. The size, location, and temporal relationship to clinical findings of large and small vessel infarcts were recorded. Infarcts determined to represent acute or subacute processes proximal to death were not included in further analyses. Microvascular disease (arteriosclerosis) and microinfarcts were assessed using a semiquantitative grading scale (none, mild, moderate, and severe) according to the National Alzheimer Coordinating Center Neuropathology Data Manual Version 1.0 (available at https://www.alz.washington.edu /NONMEMBER/PDF/npded2004.pdf). The presence or absence of vascular contributions to cognitive decline in these patients was then dichotomized to either present or absent according to consensus agreement between 2 examining neuropathologists (J.E.P. and D.W.D.), as described previously.30 Argyrophilic grain disease (Braak disease) was characterized by the presence of hippocampal amyloid and amyloid angioid silver- and tau-positive grains, as well as tau-positive coiled bodies in white matter, and amygdaloid “ballooned” neurons as confirmed with neurofilament or α-β-crystallin immunoreactivity.31

After the neuropathologic assessments, each case was classified according to current and past neuropathologic criteria: the Khachaturian criteria,32 the CERAD criteria,24 and the NIA-Reagan criteria.33 The Khachaturian criteria are most liberal with respect to meeting neuropathologic criteria for AD and focus on age-related counts of any type of plaque (DP or NP). The CERAD criteria require a semiquantitative rating of NP density as sparse, intermediate, or frequent. Neither of these sets of criteria accounts for NFTs. The NIA-Reagan criteria rate the probability of NPs and NFTs as being consistent with the neuropathologic diagnosis of AD and then make a final probabilistic assessment of low, intermediate, or high probability of AD.

During the study, 15 patients died and underwent autopsy while their clinical classification was aMCI (single or multiple domain). Postmortem, their medical histories were reviewed to determine the condition of the patients between their last clinical evaluation by the research team and their time of death. The median interval between the last clinical evaluation and death was 0.72 year (263 days), with a range of 0.19 to 1.18 years (69-430 days). Postmortem reviews confirmed that they had remained mildly impaired. Six patients died of cardiac causes, 3 of pulmonary complications, 4 of cancer, 1 of renal insufficiency, and 1 of trauma.

The demographic, clinical, and apolipoprotein E features of the 15 patients are given in Table 1. The mean (SD) age of the group at death was 88.9 (6.1) years, and their education level was 13.5 (3.9) years. The aMCI status at the final clinical evaluation was documented by a mean (SD) Mini-Mental State Examination score of 26.1 (2.0); a mean (SD) Dementia Rating Scale score of 126.4 (10.1), with impaired learning documented on the Auditory Verbal Learning Test with a cumulative mean (SD) learning score across 5 trials of 25.4 (4.6) (approximately 10th-19th percentile for age- and education-matched individuals); and mean (SD) delayed recall of 18.3% (23.6%) (0-9th percentile).34 There were 3 apolipoprotein E4 carriers among the 13 patients on whom apolipoprotein data were available. The mean (SD) time since the patients were diagnosed as having aMCI was 2.8 (2.5) years.

Braak staging for the patients with aMCI compared with the healthy and AD groups is shown in Figure 1. The modal stages for the patients with aMCI were II and III, accounting for 10 of the 15 patients. The neuropathologic data according to Braak staging; DP4, CPs, and NPs; and quantitation of Lewy bodies and vascular disease are given in Table 2. The neuropathologic classifications of the data vary according to the specific criteria used. For example, according to the Khachaturian criteria, 7...
of 15 patients with aMCI were classified as fulfilling the criteria for AD, whereas 8 were not. Assuming that the aMCI diagnosis was sufficient to fulfill the clinical impairment criteria required by the CERAD, 3 patients with aMCI were classified by CERAD criteria as having probable AD, and another 2 had possible AD. However, 10 of the patients had insufficient neuropathologic findings to classify them as having AD by CERAD criteria.

Figure 2 shows the frequency of participants in all 3 groups meeting the criteria for low, intermediate, or high likelihood of having AD by NIA-Reagan criteria. Most of the patients with MCI (n=11) had a low likelihood of having AD, whereas 3 had an intermediate and 1 a high likelihood of having AD.

For comparison, the neuropathologic data for the healthy and probable AD groups are also given in Table 2
and Figures 1 and 2. In general, for the healthy individuals, most had Braak stages of I to III and a 0 (none) or 1 (sparse) rating of DPs. Cored plaques were uncommon, with a mean (SD) score of 0.68 (0.77), and NPs were very uncommon, with a mean (SD) score of 0.36 (0.56); the modal number of NPs was 0 (13 of 28) (Table 2 and Figure 3). In contrast, the age-matched patients with AD showed a Braak stage of IV to V, with a mean DP score of 2.91 (0.29) and frequent CPs (mean [SD], 2.57 [0.59]) and NPs (mean [SD], 1.91 [1.08]) (Table 2 and Figure 3).

Some patients with aMCI had other concomitant neuropathologic features, which likely contributed to the clinical presentations of the patients. In particular, there was argyrophilic grain disease in 7 patients with aMCI,31,35 with the extent of involvement ranging from occasional grains in the medial temporal lobe to argyrophilic grains constituting the major pathologic abnormality (patient 2). In other patients, argyrophilic grains were seen in conjunction with NFTs (patients 6, 9, and 10), DPs (patient 3), or hippocampal sclerosis (patients 5 and 11) (Table 2).
Concomitant vascular disease was seen in 5 patients, with definite contributions to cognitive decline in only a single patient (patient 6) and another 4 patients with possible contributions (patients 3, 7, 8, and 13). Hippocampal sclerosis was seen in 3 patients, alone in patient 15 and with argyrophilic grains in patients 5 and 11. Finally, a few patients were classified as having neuropathologic AD, including 3 who met intermediate probability (patients 4, 7, and 14) and 1 who met high probability (patient 13) for AD by NIA-Reagan criteria (Table 2). None of the patients had definite AD abnormalities with a high Braak stage and frequent NPs (by CERAD criteria).

Figure 4 shows amyloid and neurofibrillary pathologic features for typical healthy, aMCI, and AD cases.

**COMMENT**

These data describe in detail the neuropathologic findings of prospectively characterized and longitudinally followed patients who died while their clinical diagnosis was aMCI compared with similar patients with AD and individuals with no cognitive impairment. We found that the regional involvement by NFTs correlated best with the degree of clinical impairment across the spectrum of healthy to aMCI to AD. In contrast, the amyloid plaque burden was less discriminating. In general, patients with AD had more CPs and NPs, whereas the amyloid burden of patients with aMCI was more similar to that of the healthy individuals. Thus, it may be that the transition to dementia occurs when neurofibrillary abnormalities spread beyond the medial temporal lobe. Several demographic features of these patients are noteworthy. They were quite old (mean age, 89 years). The prevalence of apolipoprotein E4 carriers was low at 3 of 13, and 1 of these had the 2/4 genotype. This likely reflects the advanced age of this group. These patients met the clinical criteria for aMCI and had normal indices of general cognitive function for age on the Mini-Mental State Examination and the Dementia Rating Scale, with relative impairment in learning and recall as characterized by Auditory Verbal Learning Test performance.

The predominant location of 1 or more of several neuropathologic features was in medial temporal lobe structures, and that likely accounted for the memory impairments seen in these patients clinically. Typically, these changes consisted of NFTs in the entorhinal cortex and hippocampal formation that can be seen in early incipient AD. Many cases had the deposition of diffuse amyloid in the neocortex, with relatively few NPs and a Braak stage of III or less. This constellation of findings has been referred to as pathologic aging by some investigators, but its true role in the distinction between normal aging and AD is uncertain.27 Most of the cases were characterized by the neuropathologists as having prodromal or incipient AD, meaning that they did not fulfill the criteria for AD but were suggestive of being in transition (diffuse amyloid in the neocortex and frequent NFTs in medial temporal lobe structures). The role of argyrophilic grains in AD development is not known, but a recent study36 suggests that more than 25% of patients with AD have argyrophilic grains, and increased frequency of argyrophilic grain disease in AD with 4R tau-specific immunohistochemical findings has also been reported. Hippocampal sclerosis is not believed to be on the AD spectrum, but it may be related to ischemic factors and neurodegeneration in others.37,38

Because the sets of neuropathologic criteria for AD range from the most liberal (Khachaturian) to intermediate (CERAD) to the most restrictive (NIA-Reagan), the proportion of patients with aMCI classified as AD diminished. That is, if the relatively loose Khachaturian criteria for AD were invoked recognizing age-adjusted counts of any form of amyloid plaque, 7 of 13 patients with aMCI met the criteria for AD. However, even with this most liberal set of criteria, fewer than 50% of the group would be classified as having AD. Using CERAD criteria, which emphasizes NPs, only 5 of 15 patients met the criteria.
for possible or probable AD. Using the currently accepted NIA-Reagan criteria for AD, including NPs and NFTs, only 1 patient was believed to have a high probability of representing AD changes, 3 had intermediate probability, and the rest had low or no probability. The Braak staging corroborated this classification, with most patients being between Braak transentorhinal and limbic stages. Typically, a Braak stage IV is believed to be compatible with AD. Therefore, most patients had “AD tendencies” but did not meet the criteria for definite AD.

It should be noted, however, that there was a considerable amount of heterogeneity in the neuropathologic findings. Many patients had some argyrophilic grain disease. This has been noted by Braak and Braak, Tolnay et al, and others, but the relationship of the grain abnormality to clinical symptoms is unclear. It is likely that argyrophilic grains were an incidental finding in some patients and, in a few, may have been the primary pathologic abnormality. Hippocampal sclerosis was also present in a few patients, and it is accepted that this entity can produce clinical features similar to those of incipient AD. Finally, several patients had features of subcortical ischemic-vascular disease.

The healthy and AD comparison groups provide an interesting contrast for the interpretation of the neuropathologic features of aMCI. Comparing the various types of plaques (DP, CP, and NP), it is apparent that the patients with MCI seem more like the healthy individuals than those with AD. With respect to NFT distribution as measured by Braak staging, the MCI group seemed more advanced. These findings complement neuropathologic studies on early AD. An important recent article from the Nun Study explored the relationship between AD neurofibrillary pathologic features and intermediate stages of cognitive impairment. These investigators found a strong relationship between neurofibrillary pathologic features and cognitive state across the clinical spectrum, but they also noted that by excluding other non-AD abnormalities, they may not be able to explain the total spectrum of findings. Approximately 50% of their total group was excluded for having non-AD abnormalities. They also commented that the clinical classification system used in the Nun Study may have underestimated the degree of impairment in their patients, who were slightly more impaired than the patients with aMCI in the present study. The Religious Orders Study found that 44% of their patients with MCI had a low likelihood of AD pathologic abnormalities, and another 44% had an intermediate likelihood according NIA-Reagan criteria. However, the MCI diagnosis in the Religious Orders Study was different from the current aMCI criteria and allowed for impairment in multiple cognitive domains and may have included patients who were more impaired than the present group. More recently, data from the Religious Orders Study have documented an intermediate level of AD and vascular abnormalities in their patients with MCI using a broader definition of multiple-domain MCI.

A study from Washington University describing the neuropathologic features of patients with very mild AD (Clinical Dementia Rating of 0.5) demonstrated that 84% of these patients had neuropathologic features of AD. This study does not necessarily contradict the findings of the present study because the patients in the Washington University study were demented at the time of death, and this group uses modified Khachaturian criteria for the neuropathologic diagnosis of AD, which are far more liberal than those used herein. This research group does not use the MCI classification and focuses on patients with very mild clinically probable AD. In so doing, they demonstrated that when most of their patients with mild AD underwent autopsy, most had features of AD neuropathologically.

A study investigating the distribution of NFTs and amyloid plaques in 5 healthy individuals and 3 patients with MCI reached conclusions similar to ours. These investigators found that the NFT distribution followed a hierarchical pattern and correlated with memory performance, whereas the density of amyloid plaques did not.

There are limitations to the present study. The number of patients who died while their clinical classification was aMCI was small. Our patients were quite old. Individuals who die and undergo autopsy while in the aMCI state may not represent the universe of all patients with MCI. A study that evaluates the neuropathologic outcome of patients who once were classified as aMCI but subsequently progressed to another diagnosis may represent the more typical MCI case.

In summary, although the concept of aMCI remains under study, data are converging on the clinical characterization, rates of progression, clinical predictors, and now the neuropathologic substrate. This study provides data on individuals who died while their clinical classification was aMCI and contributes to our understanding of the neuropathologic substrate of these patients.

Accepted for Publication: September 8, 2005.

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Funding/Support: This work was funded by the National Institute on Aging, grant U01 AG06786 from the Mayo Alzheimer’s Disease Patient Registry, and grant P50 AG16574 from the Mayo Alzheimer’s Disease Research Center and the Robert H. and Clarice Smith and Abigail van Buren Alzheimer’s Disease Research Program.

Acknowledgment: We thank Donna Asleson and Dorla Burton for their expert secretarial assistance in the preparation of this manuscript and our other colleagues in the Alzheimer’s Disease Research Center, in particular, Ruth Cha, MS, for statistical analysis.
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