Background: The pathologic outcome of patients diagnosed with mild cognitive impairment (MCI) following progression to dementia is poorly understood.

Objective: To determine the pathologic substrates of dementia in cases with prior diagnosis of amnestic MCI.

Design and Setting: Community-based cohort.

Patients: Thirty-four subjects followed up prospectively as part of a community-based study who were diagnosed with amnestic MCI, progressed to clinical dementia, and underwent subsequent postmortem brain analysis.

Main Outcome Measures: Neuropathologic analyses resulted in assignment of a primary pathologic diagnosis and included staging of Alzheimer pathologic abnormalities and identification of contributing vascular disease, Lewy bodies, and argyrophilic grains.

Results: Although the majority of subjects progressed both clinically and pathologically to Alzheimer disease (AD), 10 (29%) of them developed non-AD primary pathologic abnormalities. All of the cases were found to have sufficient pathologic abnormalities in mesial temporal lobe structures to account for their amnestic symptoms regardless of the cause. Most subjects were found to have secondary contributing pathologic abnormalities in addition to primary pathologic diagnoses. No significant differences between subjects with and without neuropathologically proven AD were detected in demographic variables, apolipoprotein E genotype, or cognitive test measures at onset of MCI, onset of dementia, or last clinical evaluation.

Conclusions: The neuropathologic outcome of amnestic MCI following progression to dementia is heterogeneous, and it includes AD at a high frequency. Complex neuropathologic findings including 2 or more distinct pathologic entities contributing to dementia may be common in community-based cohorts. Neither demographic variables nor cognitive measures had predictive value in determining which patients diagnosed with MCI will develop the neuropathologic features of AD.

Arch Neurol. 2006;63:674-681

THE CONCEPT OF MILD COGNITIVE IMPAIRMENT (MCI) has become a focus for study of the evolution of Alzheimer disease (AD). Early identification of patients destined to develop AD will allow for earlier intervention in an attempt to slow or halt the progression of disease. Clinically, subtypes of MCI have been recognized, with the amnestic subtype (aMCI) having an elevated risk of progressing to clinical AD. It is unclear whether the clinical diagnosis of aMCI predicts progression to pathologic AD. Pathologic confirmation of AD in these cases is important to validate these clinical observations and to justify our use of treatments for AD in aMCI.

Several small studies focusing on postmortem neuropathologic evaluation of MCI cases have concluded that many of these patients exhibit typical AD changes, including both neurofibrillary tangles and neuritic plaques. Not all cases of MCI show these changes, suggesting that pathologic heterogeneity exists. Cases of MCI with neuropathologic findings that range from a complete absence of significant AD pathologic abnormalities to sufficient pathologic abnormalities to warrant a firm neuropathologic diagnosis of AD have been reported. Other cases with predominant neuropathologic findings consistent with the diagnoses of vascular dementia, dementia with Lewy bodies, and argyrophilic grain disease (AGD) have been reported. The presence of neurofibrillary tangles and neuritic plaques in cognitively normal individuals further complicates the neuropathologic analysis, making

For editorial comment see also page 647
the assessment of AD pathologic abnormalities quantita-
tively rather than absolutely. Detailed neuropatho-
logic analyses need to be performed to validate the con-
clusion that aMCI represents early AD pathologically.
Large-scale neuropathologic studies of aMCI are lacking
owing to limited brain tissue availability.

An alternative strategy addressing the issue of clinico-
pathologic correlation in aMCI includes neuropatho-
logic analysis of patients with aMCI who are prospect-
vively followed up and have converted to dementia.
These patients would be expected to show full develop-
ment of the neuropathologic features underlying the
cognitive impairment. This would facilitate the quantita-
tive assessment of AD pathologic abnormalities as well
as allow for higher sensitivity in detecting possible con-
tributing pathologic abnormalities. Currently, such stud-
ies are lacking in the literature. Our study was under-
taken to clarify unanswered questions and concerns
related to the pathologic outcome of subjects progress-
ing from aMCI to dementia.

CLINICAL EVALUATION

We identified all of the subjects enrolled in the Mayo Alzhei-
mer Disease Patient Registry community-based cohort who were
diagnosed with aMCI from 1993 to 2001, were prospectively
followed up, converted to dementia, and underwent neuro-
pathologic examination. Nonamnestic forms of MCI were
excluded from the present analysis. Neurologic testing, neu-
ropsychologic examinations, neuroimaging, and laboratory
analyses were performed at entry into the Mayo Alzheimer Dis-
ease Patient Registry and then annually or biennially during
the follow-up period. Clinical diagnosis was determined by a
consensus committee comprising neurologists, neuropsycholo-
gists, a neuropsychiatrist, nurse specialists, and a geriatrician
following review of all of the available data. Inclusion criteria
for the present analysis included a prospectively determined
diagnosis of aMCI on at least 1 consensus evaluation, sub-
sequent progression to clinical dementia, and neuropathologic
evaluation. These studies have been approved by the Mayo In-
stitutional Review Board, Rochester, Minn.

Clinical criteria for the diagnosis of aMCI included a memory
problem, intact general cognitive functions and activities of daily
living, evidence of cognitive dysfunction with predominant
memory involvement on formal testing, and absence of de-
mentia. Specific neuropsychologic cutoff scores were not used;
rather, the subjects were diagnosed with aMCI if their memory
performance was impaired out of proportion to their other cog-
nitive domains as described previously. Cases were subclass-
sified into single-domain or multiple-domain aMCI according
to published criteria. Cognitive impairment in attention and
executive function, language skills, or visuospatial skills in ad-
tion to memory impairment was used to classify subjects as
having multiple-domain aMCI. We used Diagnostic and Statis-
tical Manual of Mental Disorders, Revised Third Edition or Di-
agnostic and Statistical Manual of Mental Disorders, Fourth Edi-
tion criteria for the diagnosis of dementia, and we used the
National Institute on Neurologic and Communicative Disor-
ders and Stroke/Alzheimer Disease and Related Disorders As-
association criteria for the diagnosis of AD. Cognitive screen-
ing measures included the Mini-Mental State Examination,
Kokmen Short Test of Mental Status, Clinical Dementia Rating
scale, Global Deterioration Scale, and Mattis Dementia
Rating Scale. Apolipoprotein E (APOE) genotyping was per-
formed on blood samples according to established protocols.

AUTOPSY PROCEDURE

The brains were processed in accordance with the recommenda-
tions of the Consortium to Establish a Registry for Alzhei-
er’s Disease (CERAD). Brain tissue from the left hemisphere
was fixed in 10% to 15% buffered formalin for 7 to 10 days.
Brain areas that were sampled included superior and middle
frontal gyrus (plane just anterior to temporal tip), superior and
middle temporal gyrus (plane of mammillary body), inferior par-
tial lobe (plane 1 cm behind posterior pole of splenium),
calcarine (primary visual) cortex, anterior cingulate (plane of
anterior commissure), hippocampus with adjacent inferior tem-
poral cortex (level of the lateral geniculate body), amygdala and
entorhinal cortex (level of the mammillary bodies), nucleus ba-
salis, basal ganglia, cerebellum, thalamus with subthalamic
nucleus, midbrain (with substantia nigra), pons (with locus coe-
ruleus), and cerebellum as well as representative sections of
any lesions noted grossly. Following routine processing in par-
affin and cutting, sections were stained with hematoxylin-
cosin. Selected sections were stained with modified Biel-
schowsky, Luxol fast blue and periodic acid–Schiff, and thi-
oflavin-S and immunostained for β-amyloid (clone 6F3D;
Novocastra, Newcastle upon Tyne, England), phosphorylated
tau (clone AT8; Endogen, Woburn, Mass), 4-repeat tau (ET3,
recognizing exon 10 of the tau protein specifically; a gift from
Peter Davies, PhD, Albert Einstein College of Medicine, Bronx,
NY), α-synuclein (clone LB509; Zymed Laboratories, San Fran-
cisco, Calif), ubiquitin (polyclonal; Dako, Glostrup, Den-
mark), neurofilament protein (clone 2F11; Dako), α-β-
crystallin (polyclonal; Chemicon, Temecula, Calif), and glial
fibillary acid protein (polyclonal; Dako).

NEUROPATHOLOGIC ASSESSMENT

Neuropathologic evaluation included classification according
to criteria by Khachaturian, CERAD, National Institute on
Aging and Reagan Institute Working Group on Diagnostic
Criteria for the Neuropathological Assessment of Alzheimer’s
Disease, and Braak staging of neurofibrillary degeneration.
Clinical information was available to the neuropathologist to
assist in the final determination of CERAD assignment. Size,
location, and histologic age of large and small vessel infarcts
were recorded. Acute or subacute infarcts were not considered
clinically significant with respect to chronic antemortem neu-
rologic features. Microvascular disease, microinfarcts, amyloid
angiopathy, and intracranial atherosclerosis were assessed
using semiquantitative grading scales according to the
National Alzheimer Coordinating Center protocol. The pres-
ence or absence of vascular contributions to cognitive decline
in these subjects was then dichotomized as being either
present or absent according to consensus agreement between
2 examining neuropathologists (J.E.P. and D.W.D.). Lewy
body pathology was analyzed on α-synuclein–immunostained
sections and was categorized as brainstem, limbic, or neocor-
tical. Argyrophilic grain disease was visualized with both
Gallyas stain and the ET-3 monoclonal antibody, and it was
included as a pathologic diagnosis only if there was significant
involvement of the medial temporal lobe, evidence for tau-
positive coiled bodies in white matter, and “ballooned” neu-
rons in the amygdala.

Following review by the 2 neuropathologists, a consensus
diagnosis was rendered, taking into account the dominant neu-
ropathologic features and the relative contributions of the neu-

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pairment and diagnosis of dementia. Final consensus neuropathologic diagnosis (AD vs non-AD) was used to group subjects for within-group and comparative analyses.

**STATISTICAL ANALYSIS**

Rank sum test, Fisher exact test, and \( \chi^2 \) tests were used to compare both quantitative and categorical aspects of the clinical and neuropathologic findings. \( P<.05 \) was considered statistically significant.

**RESULTS**

Thirty-five subjects fulfilled entry criteria. One patient meeting the criteria described earlier was excluded from the analysis, as the autopsy findings were rendered uninterpretable by the coincident development of a high-grade infiltrative astrocytoma. The demographic features of the study cohort are shown in Table 1. No significant differences were found between neuropathologically confirmed AD and non-AD groups for any of the demographic variables studied.

All of the 34 subjects had memory impairment at the time of initial diagnosis of MCI. Twenty-four subjects initially had isolated memory impairment and were classified as having aMCI.1-3 The remaining 10 subjects had

### Table 1. Demographic Analysis*

<table>
<thead>
<tr>
<th>Demographic</th>
<th>AD Cases (n = 24)</th>
<th>Non-AD Cases (n = 10)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death, mean, y</td>
<td>89.5</td>
<td>87.5</td>
<td>89.0</td>
</tr>
<tr>
<td>Male/female, No.</td>
<td>7/17</td>
<td>4/6</td>
<td>11/23</td>
</tr>
<tr>
<td>Duration of MCI, mean, mo</td>
<td>31.3</td>
<td>34.1</td>
<td>32.3</td>
</tr>
<tr>
<td>Duration of dementia, mean, mo</td>
<td>32.0</td>
<td>32.9</td>
<td>32.9</td>
</tr>
<tr>
<td>Duration of follow-up, mean, mo</td>
<td>85.7</td>
<td>68.8</td>
<td>78.3</td>
</tr>
<tr>
<td>Education, mean, y</td>
<td>14.0</td>
<td>13.5</td>
<td>13.5</td>
</tr>
<tr>
<td>APOE-ε4 genotype, No. (%)</td>
<td>10 (41.7)</td>
<td>4 (40.0)</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td>Clinical diagnosis of AD, No. (%)</td>
<td>21 (87.5)</td>
<td>7 (70.0)</td>
<td>28 (82.4)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment. *Between-group comparisons using rank sum and Fisher exact tests showed no significant differences between neuropathologically confirmed AD and non-AD cases.

### Table 2. Clinical and Demographic Data

<table>
<thead>
<tr>
<th>Subject No./Sex/Age at Death, y</th>
<th>Duration of MCI, mo</th>
<th>Duration of Dementia, mo</th>
<th>Duration of Enrollment in ADPR, mo</th>
<th>Education, y</th>
<th>APOE Genotype</th>
<th>Presenting Diagnosis</th>
<th>Final Clinical Diagnosis</th>
<th>Contributing Diagnoses</th>
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<tr>
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<td>16.6</td>
<td>1.2</td>
<td>93.7</td>
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<td>33</td>
<td>aMCI-MD</td>
<td>Other Vascular</td>
<td></td>
</tr>
<tr>
<td>2/F/100</td>
<td>16.4</td>
<td>51.9</td>
<td>68.3</td>
<td>16</td>
<td>33</td>
<td>aMCI</td>
<td>AD</td>
<td>None</td>
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<tr>
<td>3/F/103</td>
<td>49.6</td>
<td>9.2</td>
<td>58.8</td>
<td>15</td>
<td>34</td>
<td>aMCI</td>
<td>AD</td>
<td>None</td>
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<tr>
<td>4/F/98</td>
<td>148.6</td>
<td>7.7</td>
<td>156.3</td>
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<td>23</td>
<td>aMCI</td>
<td>Other Vascular, vitamin B12 deficiency</td>
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<td>Vascular</td>
</tr>
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<td>AD</td>
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</tr>
<tr>
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<td>61.3</td>
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<td>AD</td>
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<td>AD</td>
<td>PD</td>
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<tr>
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<td>135.8</td>
<td>158.2</td>
<td>16</td>
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<td>AD</td>
<td>None</td>
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<tr>
<td>12/F/88</td>
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<td>AD</td>
<td>Depression</td>
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<td>31.7</td>
<td>101.7</td>
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<td>aMCI-MD</td>
<td>AD</td>
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<tr>
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<td>24.0</td>
<td>89.4</td>
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<td>aMCI</td>
<td>AD</td>
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</tr>
<tr>
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<td>36.0</td>
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</tr>
<tr>
<td>16/M/84</td>
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<td>AD</td>
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</tr>
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<td>113.4</td>
<td>128.9</td>
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<td>AD</td>
<td>Vascular</td>
</tr>
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<td>19/M/89</td>
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<td>49.8</td>
<td>128.3</td>
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<td>33</td>
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<td>AD</td>
<td>Vascular</td>
</tr>
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<td>Depression</td>
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<td>61.7</td>
<td>92.5</td>
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<td>34</td>
<td>aMCI</td>
<td>AD</td>
<td>Depression</td>
</tr>
<tr>
<td>25/M/96</td>
<td>39.3</td>
<td>11.9</td>
<td>51.3</td>
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<td>33</td>
<td>aMCI-MD</td>
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</tr>
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<td>28.9</td>
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<td>AD</td>
<td>Vascular</td>
</tr>
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<td>28/F/89</td>
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<td>48.6</td>
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<td>PD</td>
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<td>29/F/73</td>
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<td>52.8</td>
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<td>Depression</td>
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<td>46.3</td>
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<td>Trauma</td>
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<td>53.9</td>
<td>80.6</td>
<td>8</td>
<td>24</td>
<td>aMCI-MD</td>
<td>AD</td>
<td>None</td>
</tr>
<tr>
<td>Median age of 89 y*</td>
<td>32.3</td>
<td>32.9</td>
<td>78.3</td>
<td>13.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; ADPR, Alzheimer Disease Patient Registry; aMCI, amnestic mild cognitive impairment; MD, multiple domain; NA, not applicable; PD, Parkinson disease.

*Values are expressed as the median.
deficits in other cognitive domains in addition to memory impairment and were classified as having multiple-domain aMCI.

As required by the entry criteria for this analysis, all of the subjects became demented over the course of clinical follow-up. Of the 24 subjects with aMCI, 19 received a final clinical diagnosis of AD; 9 of the 10 subjects with multiple-domain aMCI also had final clinical diagnoses of AD. Two subjects were given the clinical diagnosis of vascular dementia, and 1 was thought to have progressed to dementia with Lewy bodies. In 3 cases, the dementia was considered difficult to classify. Sixteen of the 34 subjects were thought to have additional contributing clinical diagnoses (Table 2).

The final consensus neuropathologic diagnosis of AD was assigned to 24 (71%) of 34 total subjects, 18 (75%) of 24 subjects who initially had aMCI, 6 (60%) of 10 subjects who had multiple-domain aMCI, and 21 (75%) of 28 subjects with the final clinical diagnosis of AD. The group of subjects with non-AD pathologic diagnoses included 3 subjects with Lewy body disease, 2 with hippocampal sclerosis, 2 with nonspecific tautopathy (1 of whom also hadBinswanger disease), and 1 each with AGD, frontotemporal lobar degeneration with hippocampal sclerosis, and progressive supranuclear palsy (Table 3).

The neuropathologic analysis is shown in Table 4 and Table 5. There was variable expression of AD pathologic abnormalities among cases given non-AD pathologic diagnoses. Twenty-eight (82%) of the 34 subjects had 2 or more pathologic processes that were thought to contribute to the dementia. Twelve subjects (33%) had
diagnosis of dementia. A high probability of AD, and yes refers to moderate or high probability of AD. In the Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer’s Disease.

“According to the CERAD scoring system, “no” refers to not AD or possible AD, and “yes” refers to probable or definite AD.

†According to Braak staging criteria, no refers to a Braak stage of I or II, and yes refers to a Braak stage of III, IV, V, or VI.

‡According to Braak staging criteria, no refers to a Braak stage of I or II, and yes refers to moderate or high probability of AD.

§Presence of vascular lesions determined to have contributed to the diagnosis of dementia.

<p>| Table 4. Neuropathologic Features of Pathologically Diagnosed Alzheimer Disease and Non–Alzheimer Disease Cases |
|----------------------------------------|------------------|------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Neurpathologic Feature</th>
<th>AD Cases, No. (%)</th>
<th>Non-AD Cases, No. (%)</th>
<th>P Value (Fisher Exact Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khachaturian criteria for AD</td>
<td>24 (100.0)</td>
<td>3 (30.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CERAD criteria for AD†</td>
<td>18 (75.0)</td>
<td>1 (10.0)</td>
<td>.001</td>
</tr>
<tr>
<td>NIA-Reagan criteria for AD†</td>
<td>22 (91.7)</td>
<td>1 (10.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Braak staging criteria for NFT†‡</td>
<td>23 (95.8)</td>
<td>5 (50.0)</td>
<td>.005</td>
</tr>
<tr>
<td>Vascular lesions present§</td>
<td>9 (37.5)</td>
<td>3 (30.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>AGD present</td>
<td>13 (54.2)</td>
<td>5 (50.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Lewy bodies present</td>
<td>4 (16.7)</td>
<td>5 (50.0)</td>
<td>.08</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; AGD, argyrophilic grain disease; CERAD, Consortium to Establish a Registry for Alzheimer Disease; NFT, neurofibrillary tangle; NIA-Reagan, National Institutes of Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer’s Disease.

The majority of patients initially diagnosed with aMCI who went on to develop dementia progressed both clinically and pathologically to AD. However, not all of the cases progressing from aMCI to dementia developed the clinical or pathologic features of AD. Multiple pathologic abnormalities were also present within some cases. Our study highlights the heterogeneous pathologic outcomes of aMCI following progression to dementia in a community-based cohort. The presence of cognitive impairments in addition to memory problems did not seem to predict who would have AD pathologically. These data raise the question of potential pathologic heterogeneity of subjects recruited into diagnostic and therapeutic trials in MCI.

Current evaluation of AD pathologic abnormalities in postmortem samples can be performed using criteria by Khachaturian, CERAD, National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer’s Disease, or Braak staging. These criteria have been developed with the goals of improved diagnostic accuracy and the development of universal standards. Using all of the 4 neuropathologic criteria, our data clearly demonstrate a high variability in clinico-pathologic correlation rates depending on the neuropathologic criteria used (88% using CERAD criteria to 68% using National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer’s Disease criteria). The use of different rating scales for assessment of AD pathologic abnormalities limits comparisons between studies. The provision of data using all of the current AD pathologic rating scales allows these data to be interpreted within the context of other reports in the literature.

These data support previous studies suggesting that pathologic abnormalities in the medial temporal lobe are the neuropathologic substrate for aMCI. The medial temporal lobe pathologic abnormality in the majority of cases was Alzheimer-type neurofibrillary degeneration. While neurofibrillary degeneration confined to limbic regions (Braak stages III-IV) can be seen in cognitively normal individuals, it is often associated with cognitive and functional impairment sufficient to meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for dementia in others. Several cases in this series did not have significant neurofibrillary degeneration in limbic regions; rather, other pathologic processes including hippocampal sclerosis, AGD, and frontotemporal lobar degeneration were present. Overall, the same pathologic features seen in fully developed dementia after progression from aMCI are seen in a milder form in cases coming to autopsy with the clinical diagnosis of aMCI. Studies from other centers addressing clini-co-pathologic correlations in MCI have also shown similar results taking the variations in clinical and neuropathologic criteria used into account. Just as the clinical

significant vascular disease (Table 6), 18 (53%) had AGD, and 9 (26%) had Lewy body disease.

No significant differences in cognitive measures or clinical scales were seen between cases with neuropathologically proven AD and those with other neuropathologic diagnoses. Between-group comparisons at onset of MCI, followed by aMCI, crossover to dementia, and final evaluation prior to death for all of the clinical variables are shown in Table 7.

Table 5. Neuropathologic Features of Cases Initially With an Isolated Amnestic Syndrome vs Those With Cognitive Impairment Involving Multiple Domains

<p>| Table 5. Neuropathologic Features of Cases Initially With an Isolated Amnestic Syndrome vs Those With Cognitive Impairment Involving Multiple Domains |
|----------------------------------------|------------------|------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Neurpathologic Feature</th>
<th>Amnestic MCI Cases, No. (%)</th>
<th>Multiple-Domain MCI, No. (%)</th>
<th>P Value (Fisher Exact Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus pathologic diagnosis of AD</td>
<td>18 (75.0)</td>
<td>6 (60.0)</td>
<td>.43</td>
</tr>
<tr>
<td>Khachaturian criteria for AD</td>
<td>20 (83.0)</td>
<td>7 (70.0)</td>
<td>.39</td>
</tr>
<tr>
<td>CERAD criteria for AD†</td>
<td>15 (62.5)</td>
<td>3 (30.0)</td>
<td>.13</td>
</tr>
<tr>
<td>NIA-Reagan criteria for AD†</td>
<td>18 (75.0)</td>
<td>9 (50.0)</td>
<td>.23</td>
</tr>
<tr>
<td>Braak staging criteria for NFT†‡</td>
<td>20 (83.0)</td>
<td>8 (80.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Vascular lesions present§</td>
<td>8 (33.3)</td>
<td>4 (40.0)</td>
<td>.71</td>
</tr>
<tr>
<td>AGD present</td>
<td>12 (50.0)</td>
<td>6 (60.0)</td>
<td>.72</td>
</tr>
<tr>
<td>Lewy bodies present</td>
<td>6 (25.0)</td>
<td>3 (30.0)</td>
<td>.99</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; AGD, argyrophilic grain disease; CERAD, Consortium to Establish a Registry for Alzheimer Disease; MCI, mild cognitive impairment; NFT, neurofibrillary tangle; NIA-Reagan, National Institutes of Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer’s Disease.

*According to the CERAD scoring system, “no” refers to not AD or possible AD, and “yes” refers to probable or definite AD.

†According to the NIA-Reagan scoring system, “no” refers to not AD or low probability of AD, and yes refers to moderate or high probability of AD.

‡According to Braak staging criteria, no refers to a Braak stage of I or II, and yes refers to a Braak stage of III, IV, V, or VI.

§Presence of vascular lesions determined to have contributed to the diagnosis of dementia.
expression of MCI appears to represent an intermediate state between normal cognition and dementia reflecting medial temporal lobe dysfunction, the neuropathologic expression of MCI appears to be correlated with medial temporal pathologic abnormalities.

The pathologic heterogeneity observed in our study was similar to heterogeneity seen in cases that underwent autopsy with a final clinical diagnosis of aMCI. Several of the aMCI cases had evidence of hippocampal sclerosis or AGD in addition to Alzheimer-type pathologic abnormalities, suggesting that anatomy of neurodegeneration is more predictive of the clinical syndrome than the specific pathologic process. That which unites these various processes is their predilection for the medial temporal lobe dysfunction, the neuropathologic expression of MCI appears to represent an intermediate state between normal cognition and dementia reflecting medial temporal lobe dysfunction, the neuropathologic expression of MCI appears to be correlated with medial temporal pathologic abnormalities.

The lack of a quantitative grading scale for vascular pathologic abnormalities in cognitive decline complicates a standardized interpretation of its contribution to dementia in this study; however, it is clear from the extent of vascular pathologic abnormalities and the distribution of the lesions (Table 6) that vascular disease plays an important role in the development of dementia following conversion from aMCI. Although a significant degree of variability among cases was seen for both large and small vessel infarcts, moderate to severe microvascular disease was almost universal. Only a single case had mild microvascular changes among those considered to have a vascular contribution to dementia, suggesting that microvascular disease may play a more important role in cognitive decline than overt cerebral infarction.

Table 6. Description of Vascular Disease Contributions to Dementia in 12 Cases

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Large-Vessel Infarcts</th>
<th>Lacunar Infarcts</th>
<th>Arteriosclerosis</th>
<th>Amyloid Angiopathy</th>
<th>Intracranial Atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>None</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>5</td>
<td>Right parietal (2.0 x 1.0 x 0.5 cm)</td>
<td>Left caudate</td>
<td>Moderate</td>
<td>None</td>
<td>Severe</td>
</tr>
<tr>
<td>6</td>
<td>Left basal ganglia (3.0 x 3.0 x 1.7 cm), right temporal (2.0 x 1.5 x 1.0 cm), right occipital (2.0 x 1.5 x 1.0 cm), right posterior thalamus (2.3 x 1.0 x 0.6 cm)</td>
<td>Right anterior thalamus, right caudate</td>
<td>Moderate</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>Left caudate, left occipital white matter, left hippocampus</td>
<td>Severe</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>13</td>
<td>None</td>
<td>None</td>
<td>Moderate</td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td>17</td>
<td>Right parieto-occipital (8.0 x 3.0 x 1.3 cm)</td>
<td>Right caudate, right parietal, right thalamus</td>
<td>Moderate</td>
<td>None</td>
<td>Severe</td>
</tr>
<tr>
<td>18</td>
<td>None</td>
<td>None</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>19</td>
<td>Left parietal (5.0 x 4.0 x 3.0 cm)</td>
<td>Bilateral caudate, right midfrontal, right parietal, left thalamus</td>
<td>Severe</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>20</td>
<td>None</td>
<td>Left caudate, bilateral thalamus</td>
<td>Moderate</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>26</td>
<td>None</td>
<td>Left frontal</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>31</td>
<td>None</td>
<td>None</td>
<td>Severe</td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td>34</td>
<td>None</td>
<td>Left midfrontal (2 lesions)</td>
<td>Severe</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Table 7. Clinical Measures of Pathologic AD vs Non-AD Groups at Onset of MCI, Onset of Dementia, or at Final Evaluation

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Onset of MCI</th>
<th>Onset of Dementia</th>
<th>Final Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD Cases</td>
<td>Non-AD Cases</td>
<td>Value</td>
</tr>
<tr>
<td>Mini-Mental State Examination score†</td>
<td>27.0</td>
<td>26.5</td>
<td>.88</td>
</tr>
<tr>
<td>Short Test of Mental Status score†</td>
<td>30.0</td>
<td>31.0</td>
<td>.50</td>
</tr>
<tr>
<td>Clinical Dementia Rating scale sum of boxes‡</td>
<td>1.0</td>
<td>2.0</td>
<td>.36</td>
</tr>
<tr>
<td>Clinical Dementia Rating scale global score‡</td>
<td>0.5</td>
<td>0.5</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Global Deterioration Scale score‡</td>
<td>3.0</td>
<td>3.0</td>
<td>.74</td>
</tr>
<tr>
<td>Dementia Rating Scale total raw score‡</td>
<td>123.0</td>
<td>119.0</td>
<td>.50</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment.
*Values are expressed as the median.
†Between-group comparisons and assignment of P values were based on the rank sum test.
‡Between-group comparisons and assignment of P values were based on the Fisher exact test.
No demographic or cognitive features predicted the final neuropathologic diagnoses of this cohort of subjects with dementia who transitioned from aMCI. The lack of association of apolipoprotein E status with final neuropathologic outcome may be secondary to the advanced age and low apolipoprotein E4 allele frequency in this series. Additionally, the duration of aMCI or dementia did not correlate with either the degree of AD pathologic abnormalities or the final neuropathologic diagnosis. Moreover, none of the cognitive assessment measures used in this study predicted final pathologic findings. Further research using more detailed analyses of cognitive measures and tests from the full neuropsychometric battery may be useful in predicting incipient AD, allowing further refinement in the diagnostic criteria for aMCI.

The weaknesses of this study lie not only in its small sample size but also in a potential selection bias. Although prospectively recruited as part of a community-based study, the subjects were of relatively advanced age and may not be representative of aMCI at younger ages. Moreover, as in all autopsy studies, the analysis is limited by inherent selection bias as to who comes to postmortem evaluation. The average duration of MCI was only 3 years in the study cohort, suggesting a conversion rate in excess of that reported in community-based studies of MCI.1,2,4,6,49,50 It is possible that the rapid rate of disease progression and the underlying neuropathologic characteristics seen in this study are representative of only a subset of those patients diagnosed with aMCI. Further postmortem neuropathologic studies on patients progressing through aMCI to clinical dementia will be needed to validate these findings.

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