Application of the National Institute on Aging (NIA)-Reagan Institute Criteria for the Neuropathological Diagnosis of Alzheimer Disease

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Abstract. The Khachaturian criteria and the Consortium to Establish a Registry for Alzheimer Disease (CERAD) criteria for the neuropathological assessment of Alzheimer disease (AD) emphasize senile or neuritic plaques, age, and clinical history. A new scheme stressing topographic staging of neurofibrillary changes in addition to neuritic plaques has been proposed by the National Institute on Aging (NIA)-Reagan Institute Consensus Conference. This scheme assigns cases to high, intermediate, or low likelihood categories that the dementia is due to AD. We applied this method to 84 brains from subjects with clinical and neuropathological diagnoses of AD (n = 33), non-AD dementing illnesses (n = 34), including dementia with Lewy bodies (DLB) and progressive supranuclear palsy (PSP), and no neurological disease (n = 17). We also used Khachaturian and CERAD criteria. Neurofibrillary tangle and neuritip thread densities were assessed on 6-micrometer-thick modified Bielschowsky-stained paraffin sections from entorhinal-perirhinal cortex, CA1 of hippocampus, and neocortex including inferior temporal, visual association, and primary visual cortices. Each case was assigned a Braak and Braak stage. Using the NIA-Reagan criteria, we found excellent agreement between clinical history of AD dementia and brains assigned to the high likelihood category that dementia was due to AD. Among brains diagnosed neuropathologically with other degenerative diseases, NIA-Reagan criteria were more conservative than previous criteria, and these cases were likely to be categorized as intermediate or low likelihood that dementia was due to AD. All brains from nondemented subjects were assigned to the low (81%) or intermediate (19%) categories. In summary, we found good correlation between the NIA-Reagan criteria and clinical dementia, and there was generally good agreement between these criteria and existing neuropathological methods, Khachaturian and CERAD, in diagnosing AD. In studying several other neurodegenerative diseases, such as DLB, which shows neuropathological and clinical overlap with AD, the staging of neurofibrillary changes offered potential diagnostic refinement.

Key Words: Alzheimer disease; Diagnostic criteria; Neuritic plaques; Neurofibrillary tangles; Topographic staging methods.

INTRODUCTION

Recent methods for the pathological diagnosis of Alzheimer disease (AD) have included 1) Khachaturian criteria, emphasizing neocortical plaques per unit area corrected for age, which could include diffuse as well as neuritic types (1), and 2) the Consortium to Establish a Registry for Alzheimer Disease (CERAD) criteria, stressing semiquantitative neuritic plaque counts with adjustments for age together with clinical history to give level of likelihood of AD (2). Both approaches vary the neuropathological criteria for AD according to the presence or absence of a history of clinical dementia. Although both methods acknowledge that neurofibrillary tangles may be present, neither requires their presence to make the diagnosis of AD.

In 1997, the National Institute on Aging (NIA) and the Ronald and Nancy Reagan Institute of the Alzheimer's Association suggested new guidelines for making the postmortem diagnosis of AD (3), which combine semi-quantitative assessments of both neuritic plaques and neurofibrillary tangles.

Topographic staging of Alzheimer changes, such as the method proposed by Braak and Braak (4), is recommended in the NIA-Reagan guidelines. Braak and Braak identified a predictable topographic pattern of neurofibrillary tangle accumulation involving cortical and subcortical regions in a study of 83 autopsy brains. Similar observations have been made or verified by other investigators (5–9). The Braak and Braak scheme defined 6 hierarchical stages. Neurofibrillary tangles preferentially involve the entorhinal-perirhinal cortex in Braak and Braak stages I–II. In stages III–IV, tangies also accumulate in hippocampus and other limbic regions with limited neocortical involvement. In stage V, neurofibrillary changes occur in association cortices, and in stage VI, neurofibrillary changes also occur in primary sensory cortex (4).

Assessment by NIA-Reagan guidelines directs the neuropathological differential diagnosis of dementia. The guidelines lead to a probabilistic statement that there is a low (Braak and Braak stages I–ID), intermediate (stages III–IV), or high (stages V–VI) likelihood that dementia is due to AD. The criteria for assignment to low, intermediate, or high likelihood categories do not vary with clinical history or age of the patient. As defined, these categories apply only to individuals with dementia, but the underlying guiding principle was that any degree of
Alzheimer changes is abnormal and should be recorded as such, even in instances where they appear to be clinically incidental (3). In accord with this, we also applied our implementation of the staging scheme to individuals who were not clinically demented.

The new criteria are written as a general framework with the intent that specific application will be left to practicing pathologists. Our objectives were to 1) devise a practical method of applying the new guidelines, and 2) validate them against currently accepted neuropathological methods for diagnosing AD. The initial description of Braak and Braak staging used 100-micrometer thick polyethylene glycol embedded sections stained by Gallyas or Campbell-Switzer silver techniques. We applied the principles of the Braak and Braak scheme to 6-micrometer-thick paraffin sections stained by the modified Bielschowsky silver method. We assigned stages I–VI using neurofibrillary tangle and neuripil thread assessments from 5 brain areas. We compared the results with Khachaturian and CERAD criteria in distinguishing AD from non-AD dementia and mixed dementias. We also applied all 3 schemes to brains from nondemented subjects.

MATERIALS AND METHODS

Case Selection

A total of 84 brains were examined for this study. Sixty-seven brains came from patients with neurodegenerative diseases of whom 63 were clinically demented. Control brains came from 17 nondemented subjects. To develop our application of the new guidelines, 46 cases consisting of consecutively accessioned AD (n = 10), progressive supranuclear palsy (PSP; n = 11), dementia with Lewy bodies (DLB; n = 9, 1 case of which also had histological AD), and 16 brains from nondemented individuals ages greater than 65 years were selected by neuropathological diagnosis from the files of the Massachusetts Alzheimer Disease Research Center (ADRC) Brain Bank. Subsequently, the resulting method was tested against 38 sequentially accessioned brains, obtained during the period January to June 1997, including 23 cases of AD, 5 cases of PSP including 4 nondemented patients, 6 cases of DLB, 1 case of AD with multiple system atrophy, 1 case of Pick disease, 1 case of cerebro-amyloid angiopathy with multiple infarcts, and 1 brain from a psychometrically-tested elderly control subject.

Neuropathological criteria utilized for making the original diagnosis included Khachaturian and CERAD criteria for AD (1, 2). PSP and DLB were diagnosed using published neuropathological criteria (10–12). Criteria for inclusion as a control subject included no history of neurological disease revealed during discussion with the clinicians responsible for the patient, or in review of the patient’s chart in preparation for complete postmortem examination. In addition, retrospective reviews of the medical records were performed to screen for evidence of underlying dementia or cognitive impairment. Specific information of interest, patterned after Arzriaga et al (8), included 1) independent living situation prior to hospital admission and planned for discharge; 2) no evidence of cognitive impairment during the hospitalization preceding death; and 3) no past history of cognitive impairment or relevant neurological disease (Table 1). Families of the deceased were not contacted for information.
TABLE 2
Comparison of Histological Sections in 3 AD Protocols and Comparable Sections Used in This Study

<table>
<thead>
<tr>
<th>Khachaturian</th>
<th>CERAD</th>
<th>NIA-Reagan</th>
<th>MGH ADRC***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal ctx</td>
<td>mid frontal ctx</td>
<td>mid frontal ctx</td>
<td>anterior, sup frontal ctx</td>
</tr>
<tr>
<td></td>
<td>motor ctx*</td>
<td>occipital ctx</td>
<td>posterior frontal ctx</td>
</tr>
<tr>
<td></td>
<td>HF at LGN level; uncal</td>
<td>HF and ERC</td>
<td>calcane and adjacent ctx</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>HF and ERC</td>
<td>caudate, putamen*</td>
<td>HF with LGN and temp ctx</td>
</tr>
<tr>
<td>Amygdala</td>
<td>midbrain with SN</td>
<td>thalamus*</td>
<td>caudate, putamen, nucleus accumbens</td>
</tr>
<tr>
<td>SN</td>
<td>midbrain with SN</td>
<td>SN</td>
<td>amygdala and ERC</td>
</tr>
<tr>
<td>Cerebellar ctx</td>
<td>sup, mid temp gyrri</td>
<td>locus ceruleus*</td>
<td>thalamus with centromedian nucleus</td>
</tr>
<tr>
<td>Temp ctx</td>
<td>sup temp ctx</td>
<td>cerebellum*</td>
<td>midbrain with SN</td>
</tr>
<tr>
<td></td>
<td>sup temp ctx</td>
<td>sup temp ctx</td>
<td>upper pons</td>
</tr>
<tr>
<td>Parietal ctx</td>
<td>inf parietal lobe</td>
<td>cingulate ctx*</td>
<td>cerebellum with dentate nucleus</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>inf parietal lobe</td>
<td>spinal cord*</td>
<td>temp pole</td>
</tr>
<tr>
<td></td>
<td>spinal cord*</td>
<td>mam bodies*</td>
<td>cingulate gyrus and cingulum</td>
</tr>
</tbody>
</table>

Abbreviations: ctx, cortex; mid, middle; sup, superior; HF, hippocampal formation; ERC, entorhinal cortex; LGN, lateral geniculate nucleus; temp, temporal; SN, substantia nigra; inf, inferior; mam, mamillary; *, optional sections.

** 1, adapted from reference (13).

From each neurodegenerative disease case, formalin-fixed 6-micrometer-thick, paraffin-embedded sections from standardized brain areas (13) were obtained from the Massachusetts ADRC Brain Bank (Table 2). All sections listed in Table 2, column 4, were stained with luxol-fast blue counterstained with hematoxylin and eosin (LHE) and by the modified Bielschowsky silver technique. Congo red stains were performed on selected sections, generally including at least 1 section each from frontal, parietal, and occipital cortices. From each control brain, LHE and modified Bielschowsky silver stained sections from the following areas were examined: superior/middle frontal cortex (not available on 1 control case), occipital cortex, inferior parietal cortex (not available on 3 control cases), hippocampal formation with adjacent temporal cortex, entorhinal-perirhinal cortex and amygdala, and midbrain with substantia nigra (Table 2, column 4), in addition to any gross lesions.

**Application of NIA-Reagan Criteria**

A modification of Braak and Braak staging (4) was applied to standard paraffin sections. The 3 brain sections used for staging of neurofibrillary changes were 1) entorhinal-perirhinal cortex (Brodman areas 28 and 35) at the level of amygdala and/or unc hippocampus; 2) body of the hippocampus (area CA1) at the level of the lateral geniculate nucleus containing a sample of inferior temporal cortex (Brodman area 20) lateral to the collateral sulcus; and 3) occipital lobe containing both primary visual (Brodman area 17) and visual association (Brodman area 18) cortices (Fig. 1). The density of neurofibrillary tangles and neuritic plaques was estimated in 5 areas: 1) layer II of entorhinal-perirhinal cortex; 2) CA1 of hippocampal formation; 3) inferior temporal cortex (on the same histological section as the body of the hippocampus); 4) visual association cortex; and 5) primary visual cortex.

In contrast to the approach of both the Khachaturian and CERAD methods where the highest densities of plaques are counted in specific brain regions and expressed per specified area or at a designated magnification, the Braak and Braak stage is assessed as an overall grade for a cytoarchitectural region. Each entire area of interest was evaluated to estimate the overall degree of neurofibrillary changes, including both tangies and neuritpli threads. Each area was fully examined at 250X and 1000X magnifications using a Zeiss microscope. Depending on the particular section and stain, many fields were further investigated at 2500X magnification for sharper resolution of structures. Neurofibrillary tangle and neuritpli thread densities were expressed as absent (-), rare (+), sparse (++), moderate (+++), and frequent (++++) (Table 3). After assignment of a Braak and Braak stage from I–VI, the cases were then grouped into low (stages I–II), intermediate (stages III–IV), and high (stages V–VI) likelihood categories that dementia was due to AD (Tables 4, 5).

Modified Bielschowsky silver-stained sections from frontal, temporal, and parietal cortices (Table 2, column 4) were used for Khachaturian (1) and CERAD (2) protocol evaluations. Neuritic plaque numbers were expressed as none, sparse, moderate, or frequent in the most densely-populated 1 square millimeter areas for CERAD evaluation. For Khachaturian assessment, which does not specify the type of plaque to be counted, 2 approaches were used: 1) counting only neuritic plaques, and 2) counting both neuritic and diffuse plaques in the most densely-populated 1 square millimeter areas. The plaque numbers thus obtained were used in conjunction with age and clinical history to determine the Khachaturian and CERAD assessments with respect to AD (Tables 4, 5).

**Results**

Assignment of Braak and Braak Stages

In the development of our application of the NIA-Reagan guidelines, we tested our approach on Braak and Braak's observations (4) with modifications. Summarized here is the illustration of our semiquantitative method...
used in assessing neurofibrillar changes (neurofibrillary tangles and neuritid threads) in the 5 brain areas examined for Braak and Braak staging (Figs. 2, 3).

**Stage 0:** No neurofibrillary tangles or neuritid threads were seen in the 5 areas.

**Stage I:** Rare to sparse neurofibrillary tangles and neuritid threads were seen in layer II of entorhinal-perirhinal cortex. No or rare neurofibrillary tangles and neuritid threads were seen in CA1 of hippocampal formation. No neocortical neurofibrillary tangles or neuritid threads were identified.

**Stage II:** Sparse to moderate neurofibrillary tangles and neuritid threads were seen in layer II of entorhinal-perirhinal cortex. Rare to sparse neurofibrillary tangles and neuritid threads were seen in CA1 of hippocampal formation. No or rare neurofibrillary tangles and neuritid threads were seen in inferior temporal cortex. No neurofibrillary tangles or neuritid threads were seen in visual association cortex or primary visual cortex.

**Stage III:** Moderate to frequent neurofibrillary tangles and neuritid threads were seen in layer II of entorhinal-perirhinal cortex. Sparse to moderate neurofibrillary tangles and neuritid threads were seen in CA1 of hippocampal formation. Rare to sparse neurofibrillary tangles and neuritid threads were seen in inferior temporal cortex. No neurofibrillary tangles or neuritid threads were seen in visual association cortex or primary visual cortex.

**Stage IV:** Moderate to frequent neurofibrillary tangles and neuritid threads were seen in layer II of entorhinal-perirhinal cortex. Moderate to frequent neurofibrillary tangles and neuritid threads were seen in CA1 of hippocampal formation. Sparse to moderate neurofibrillary tangles and neuritid threads were seen in inferior temporal cortex. No or rare to sparse neurofibrillary tangles and neuritid threads were seen in visual association cortex or primary visual cortex.

**Stage V:** Frequent neurofibrillary tangles and neuritid threads were seen in layer II of entorhinal-perirhinal cortex and CA1 of hippocampal formation. Moderate to frequent neurofibrillary tangles and neuritid threads were seen in inferior temporal cortex. Sparse to moderate neurofibrillary tangles and neuritid threads were seen in visual association cortex. No to rare neurofibrillary tangles and neuritid threads were seen in primary visual cortex.

**Stage VI:** Frequent neurofibrillary tangles and neuritid threads were seen in layer II of entorhinal-perirhinal cortex, CA1 of hippocampal formation, and inferior temporal cortex. Moderate to frequent neurofibrillary tangles and neuritid threads were seen in visual association areas. Rare to sparse neurofibrillary tangles and neuritid threads were seen in primary visual cortex.

The preceding semiquantitative assessments refer to the overall impression of an entire area, not simply 1 or 2 fields showing the most extreme changes. We did find cases that did not fit the scheme as well as others. There was a range of severity of changes within stages reflected by the overlap of the semiquantitative descriptors (e.g. CA1 of hippocampal formation displayed sparse to moderate neurofibrillary changes for stage III and moderate to frequent neurofibrillary changes for stage IV). When assigning stages, we relied more on the overall impression of all 5 brain areas and the distribution of changes rather than the severity of involvement of a given area.
### Table 3

<table>
<thead>
<tr>
<th>B&amp;B Stage</th>
<th>ERC</th>
<th>CA1</th>
<th>IT</th>
<th>VA</th>
<th>PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>+/++</td>
<td>−/+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>II</td>
<td>++/+++</td>
<td>+++</td>
<td>−/+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>III</td>
<td>++++/+++</td>
<td>+++</td>
<td>++/+++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>IV</td>
<td>++++/+++</td>
<td>+++</td>
<td>++++/++</td>
<td>−/++</td>
<td>−</td>
</tr>
<tr>
<td>V</td>
<td>+++++</td>
<td>+++</td>
<td>+++/+++</td>
<td>++++</td>
<td>−/+</td>
</tr>
<tr>
<td>VI</td>
<td>+++++</td>
<td>+++</td>
<td>+++/+++</td>
<td>++++</td>
<td>+/+</td>
</tr>
</tbody>
</table>

Abbreviations: B&B, Braak and Braak stage; ERC, entorhinal/perirhinal cortex layer II; CA1, Sommer's sector; IT, inferior temporal cortex; VA, visual association cortex; PV, primary visual cortex; −, absence of neurofibrillary tangles and neuritic threads; +, rare neurofibrillary tangles and neuritic threads; ++, sparse; ++++, moderate; +++++, frequent; −/+, no or rare neurofibrillary tangles and neuritic threads present.

### Table 4

Comparison of 3 Different Neuropathological Criteria for the Diagnosis of AD in Brains from 21 Non-demented Subjects

<table>
<thead>
<tr>
<th></th>
<th>NIA-Reagan</th>
<th>Khachaturian</th>
<th>CERAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Int</td>
<td>Low</td>
</tr>
<tr>
<td>Controls</td>
<td>0</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>PSP*</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

Abbreviations: Int, intermediate likelihood; A, inclusion of only neuritic plaques; B, inclusion of both neuritic and diffuse plaques; Yes, meets criteria for AD; No, does not meet criteria for AD; Def, definite AD; Prob, probable AD; Poss, possible AD. Note that 8/21 (38%) brains would meet criteria for AD counting neuritic and diffuse type plaques (Khachaturian) or possible AD (CERAD).

For example, in stages I–II, neurofibrillary changes did not extend beyond entorhinal-perirhinal cortex and CA1. For stages III–IV, significant changes did not involve neo-cortex other than the inferior temporal cortex. To assign stages V–VI, we required marked neurofibrillary involvement of inferior temporal cortex and easily identifiable tangles or threads in visual association areas, i.e., neurofibrillary changes that had progressed beyond the limbic stage. Ghost tangles, included in the assessments, were seen in all stages but were more numerous in advanced Braak and Braak stages.

Comparison of Diagnostic Methods in Nondemented Individuals (Table 4)

One goal of the NIA-Reagan criteria is to help differentiate control cases from AD. None of 21 nondemented individuals met NIA-Reagan criteria for the high likelihood category. Four of the 21 (19%) would have been assigned to the intermediate likelihood category (Braak and Braak stage III), and 17 of 21 (81%) would have been assigned to the low likelihood category if clinical dementia had been present. By contrast, both Khachaturian (if both diffuse and neuritic plaques were counted) and CERAD criteria (emphasizing only neuritic plaques) assigned 8 of the 21 (38%) subjects a diagnosis of AD, or possible AD, respectively, even without a clinical history of dementia.

Comparison of Diagnostic Methods in Individuals with A History of Dementia (Table 5)

Another goal of the NIA-Reagan criteria is to help refine the cause of dementia in demented individuals. Of 63 individuals with clinical dementia, 38 were assigned to the high likelihood category that dementia was due to AD. All 38 also met Khachaturian and 37 of 38 met CERAD neuropathological criteria for AD. Six clinically demented individuals in the high likelihood category that dementia was due to AD had concurrent neuropathological diagnoses. Four of these also met criteria for DLB, 1 brain also met criteria for PSP, and another had multiple system atrophy in addition to fulfilling AD criteria.
TABLE 5
Comparison of 3 Different Neuropathological Criteria for the Diagnosis of AD in 63 Clinically Demented Cases

<table>
<thead>
<tr>
<th>Path Dx</th>
<th>(n)</th>
<th>High</th>
<th>Int</th>
<th>Low</th>
<th>A (neuritic)</th>
<th>B (neuritic+diffuse)</th>
<th>CERAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD'</td>
<td>(33)</td>
<td>32</td>
<td>1</td>
<td>0</td>
<td>33 Yes</td>
<td>33 Yes</td>
<td>33</td>
</tr>
<tr>
<td>PSP'</td>
<td>(12)</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>4 No</td>
<td>7 No</td>
<td>3</td>
</tr>
<tr>
<td>DLB'</td>
<td>(15)</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>7 Yes</td>
<td>14 Yes</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>(3)</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1 Yes</td>
<td>2 Yes</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>(63)</td>
<td>38</td>
<td>7</td>
<td>18</td>
<td>45 Yes</td>
<td>53 Yes</td>
<td>45</td>
</tr>
</tbody>
</table>

Abbreviations: Path Dx, neuropathological diagnosis utilizing the following criteria: 1, reference (2); 2, references (10, 11); 3, reference (12); Int, intermediate likelihood that dementia is due to AD; A, inclusion of only neuritic plaques; B, inclusion of both neuritic and diffuse plaques; Yes, meets criteria for AD; No, does not meet criteria for AD; Def, definite AD; Prob, probable AD; Not, does not meet criteria for AD; Other, includes 1 case each of Pick disease, cerebral amyloid angiopathy with multiple infarcts, and multiple system atrophy combined with AD.

Khachaturian criteria were applied taking into account age, clinical history, and plaque number. The CERAD definitions of probable or possible AD considered age, clinical history, and neuritic plaque score. Note that of 16 PSP patients, 4 were not clinically demented and are not, therefore, included in this table (see Table 4).

Of the remaining 25 clinically demented individuals, 7 had an intermediate likelihood and 18 had a low likelihood that dementia was due to AD according to NIA-Reagan criteria. An alternative neuropathological diagnosis was present in 24 of the 25 cases: PSP in 11 cases, DLB in 11, Pick disease in 1 case, and amyloid angiopathy with multiple infarcts in 1 case. The 1 remaining demented case of the 25, assigned Braak and Braak stage IV, was categorized as having an intermediate likelihood that dementia was due to AD. By contrast, in the same group of 25 demented individuals, 15 met CERAD criteria for definite or probable AD (counting neuritic plaques), and 15 met Khachaturian criteria for AD (if diffuse and neuritic plaques were counted).

DISCUSSION

The NIA-Reagan criteria document provides a general strategy but few specifics for assessing the likelihood that dementia is due to AD. We first developed a simplified scheme to apply the NIA-Reagan criteria using modified Bielschowsky silver-stained sections, and then addressed several questions: 1) Do the NIA-Reagan criteria, as applied, distinguish AD from nondemented subjects? 2) How do the new criteria compare with Khachaturian and CERAD criteria in instances of clinically diagnosed dementia? 3) Do the criteria assist in differentiating AD from cases that exhibit histological overlap with AD?

Do the NIA-Reagan criteria distinguish AD from nondemented subjects? The NIA-Reagan criteria readily differentiated the 21 nondemented brains from AD brains. Thirteen of the 17 control brains had minimal neurofibrillary changes and were assigned to the low likelihood category. Of the other 4 brains assigned to the intermediate likelihood category, all Braak and Braak stage III, 1 subject was living independently prior to final hospitalization, another was totally independent 4 months prior to death and living with an elderly spouse who had suffered a stroke, a third was traveling, probably alone, on a transatlantic flight immediately preceding death due to an acute myocardial infarct. The fourth subject was evaluated by a neurologist for a neuropathy 7 months prior to death, and no cognitive difficulties were noted. Therefore, the interpretation of a Braak and Braak stage of III in an apparently cognitively normal older individual remains to be determined. In one study, brains assigned to Braak and Braak stages I–III tended to be from nondemented elderly (14); however, moderate numbers of neurofibrillary tangles in the limbic system may be associated with mild memory loss (15). Whether the presence of such changes is expected with usual aging will require the study of more prospectively evaluated elderly control subjects. As the new guidelines indicate, criteria for early or incipient AD remain to be established (3).

How do the NIA-Reagan criteria compare with Khachaturian and CERAD criteria in instances of clinically diagnosed dementia? In our implementation of the NIA-Reagan criteria, the staging of Alzheimer changes correlated well with clinical impressions and current neuropathological criteria. Of 33 cases diagnosed as "pure" AD using the Khachaturian and CERAD methods, 32 were assigned to the high likelihood category that dementia was due to AD by NIA-Reagan criteria. The only exception, assigned to the intermediate likelihood category that dementia was due to AD, was a brain from a
102-year-old man with mild dementia thought most likely to be AD and a Clinical Dementia Rating (CDR) score of 1. The Braak and Braak stage of IV suggested that AD was not fully developed in this individual.

Do the criteria assist in differentiating cases of AD from other neuropathological entities which often display overlapping pathological findings with AD? A third goal of the NIA-Reagan criteria is to assess accurately the cause of dementia in "overlap" cases. The microscopic alterations in PSP and DLB often overlap with AD in terms of the presence of neurofibrillary tangles and amyloid plaques.

Progressive Supranuclear Palsy (Tables 4, 5)

The NIA-Reagan criteria identified 13 of 16 PSP cases as low likelihood, 2 as intermediate likelihood, and 1 as high likelihood that dementia was due to AD. CERAD, requiring neuritic plaques, and Khachaturian methods categorized more of these cases as AD. Four (relying on neuritic plaques only) or 5 (including diffuse and neuritic

**Fig. 2.** Histological sections from 3 brains illustrating the spectrum of neurofibrillary changes seen in 3 of the 5 areas assessed. Photomicrographs (a–c) are from 1 brain representative of Braak and Braak stage I (NIA-Reagan low likelihood that dementia is due to AD), (d–f) represent stage III (intermediate likelihood that dementia is due to AD), and (g–i) represent stage V (high likelihood that dementia is due to AD). Sections (a), (d), and (g) are from entorhinal-perirhinal cortex, sections (b), (e), and (h) are from CA1 of hippocampus, and (c), (f), and (i) are from visual association cortex. Arrows (panel a) indicate neurofibrillary tangles. Modified Bielschowsky silver technique, 200×.
the intermediate and low likelihood groups, respectively, that dementia was due to AD. In comparison, Khachaturian and CERAD assigned more cases to the definite or probable AD categories. Seven of 15 (neuritic plaques only), or 14 of 15 cases (neuritic plus diffuse plaques), were diagnosed as AD by Khachaturian criteria, and by CERAD standards, 13 of 15 brains were assigned to definite or probable AD categories. Similar to PSP, the discordance between the NIA-Reagan criteria and existing methods is due to the importance given neocortical amyloid plaques, which may be limited to the diffuse type or a mixture of diffuse and neuritic plaques in a large subset of DBL cases (19–22). As known with PSP, some cases of DLB may coexist with AD (23). The difference in categorization of DLB cases between NIA-Reagan and Khachaturian and CERAD criteria highlights the discrepancy between plaques and the number and distribution of neurofibrillary changes in some DLB brains. The interpretation of the findings may differ among those weighting plaques more than neurofibrillary tangles in diagnosing AD. However, the inclusion of a neurofibrillary change staging scheme in such overlap cases underscores some differences that may prove to be of diagnostic significance. Use of the new criteria may, therefore, aid in differentiating a subset of AD-overlap cases from fully developed AD.

In our implementation of the NIA-Reagan criteria, demented cases with low Braak and Braak stages but substantial numbers of cortical senile plaques fell into the low or intermediate likelihood that dementia was due to AD categories, but frequently met Khachaturian or CERAD criteria for AD. The relative degree to which Alzheimer neuropathological changes and, for example, cortical Lewy bodies each contribute to dementia when both are present in an individual brain cannot be determined with certainty. The NIA-Reagan criteria highlight these overlap cases as having "low or intermediate probability that dementia was due solely (our addition) to AD," perhaps providing a nomenclature framework to begin to understand overlap syndromes and to differentiate these cases from "pure" AD in research settings. However, as illustrated by this series, even having sufficient Alzheimer changes to assign a high likelihood that dementia was due to AD does not preclude potentially relevant concurrent neuropathological diagnoses. Thus research studies on AD must take into account both the quantity of Alzheimer neuropathological changes (i.e. the Braak and Braak stage and the CERAD plaque score), as well as a careful evaluation for additional potentially confounding diagnostic considerations. While the degree to which these influence individual studies will vary, the neuropathological report should ideally provide sufficient information to assist the clinician and the investigator in assessing the likeliest contributors to dementia. The NIA-Reagan criteria appear to be a step in this direction.

Dementia with Lewy Bodies (Table 5)

Application of the NIA-Reagan criteria placed 4 of the 15 DLB cases in the high likelihood category that dementia was due to AD, with 4 and 7 cases assigned to...
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In summary, we found good correlation between the NIA-Reagan criteria and clinical dementia, and there was generally good agreement between these criteria and existing neuropathological methods, Khachaturian and CERAD, in diagnosing AD. In studying several other neurodegenerative diseases, such as DLB, which show neuropathological and clinical overlap with AD, the staging of neurofibrillary changes offered potential diagnostic refinement.

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