Neuropathologic Criteria for Diagnosing Alzheimer Disease in Persons with Pure Dementia of Alzheimer Type

Daniel W. McKeel, Jr., MD, Joseph L. Price, PhD, J. Philip Miller, Elizabeth A. Grant, PhD, Chengejie Xiong, PhD, Leonard Berg, MD, and John C. Morris, MD

Abstract. Universally accepted neuropathologic criteria for differentiating Alzheimer disease (AD) from healthy brain aging do not exist. We tested the hypothesis that Bielschowsky silver stained total, cored, and neuritic senile plaques (TSPs, CSPs, and NSPs, respectively), rather than neurofibrillary tangles (NFTs), best discriminate between the 2 conditions using rigorously defined nondemented (n = 7) and AD (n = 35) subjects with no known co-morbidities. We compared lesions in 3 neocortical regions, in hippocampal CA1, and in entorhinal cortex in 19 men and 13 women between 74 and 86 years at death. The Clinical Dementia Rating (CDR) was used to assess degree of cognitive impairment within a year of demise. Neocortical TSP measures provided the highest correlation with expiration CDR: area under the curve (AUC) = 0.986 with 97.8% sensitivity at 90% specificity with an estimated cut-point of 6.0 TSP/mm². All SP measures yielded higher estimated AUC and sensitivity for 90% specificity compared to NFTs. Derived TSP cut-points applied to 149 persons with clinical AD regardless of their neuropathologic diagnosis yielded a sensitivity of 97% and specificity of 84% for TSPs in the 3 neocortical areas. Thus cut-points based on both diffuse and neuritic SP in neocortical regions distinguished nondemented and AD subjects with high sensitivity and specificity.

Key Words: Clinical Dementia Rating; Dementia; Neurofibrillary tangles; Neuropathologic diagnosis; Receiver operating characteristic; Senile plaques.

INTRODUCTION

Histopathologic examination of the brain establishes that AD lesions are present in sufficient densities to distinguish AD from age-related neuropathology and allows detection of other dementing disorders (1). No one set of histopathologic criteria for AD, however, has been uniformly accepted by neuropathologists (2, 3). Some criteria rely on quantitative or semiquantitative determinations of senile plaque (SP) densities (4, 5), whereas other criteria emphasize neurofibrillary tangle (NFT) pathology in addition to plaque burden (6, 7). Controversy also exists about the pathologic significance of SP subtypes. Whether plaque density measures should include diffuse SPs or be restricted to neuritic plaques only is unresolved and this contributes greatly to the substantial variability among neuropathologists in determining whether AD is diagnosed (8). There is also the concern that SPs and NFTs may be only downstream pathologic phenomena whereas other changes, such as synaptic and neuronal loss, may be more relevant for the disease process (9). All currently used sets of neuropathologic diagnostic criteria for AD, however, continue to be based on SP or NFT densities (or both).

A major consideration is whether any of these criteria reliably distinguish AD from the brain changes associated with nondemented aging. Distinctions between aging and AD often have been postulated to be quantitative rather than qualitative. Arriagada et al showed that the lesion distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches that of Alzheimer’s disease and concluded that there is “a commonality in the pathologic processes that lead to NFTs and SPs in both aging and AD.” (10). This concept underlies the age-adjusted threshold of SP and NFT densities adopted by many sets of neuropathologic diagnostic criteria for AD, which assume an increase in SP and NFT density with normal aging. Alternatively, it remains possible that aging and AD may be qualitatively and quantitatively different.

Our clinicopathologic studies (11–17) find that the widespread accumulation of neocortical beta-amyloid (Aβ) in the form of diffuse and neuritic plaques is the salient neuropathological correlate of the earliest clinically detectable forms of AD (16). Subjects just at the threshold of dementia already feature large numbers of neocortical plaques, 85% of which are diffuse (primarily composed of Aβ without abnormal neurites); the remaining 15% are neuritic and possess both Aβ and dystrophic neurites. In the neocortex of nondemented subjects, plaques are either absent or present as diffuse plaques only in scattered patches. Thus, both plaque burden (density per millimeter squared) and plaque morphology appear to be useful in distinguishing the earliest detectable form of AD from nondementing aging. In contrast, the slow accumulation of NFTs that is restricted to entorhinal cortex and related medial temporal lobe structures occurs...
as a function of age and appears not to reliably distinguish AD from aging (17, 18).

Based on these findings, we hypothesized that plaque burden, but not tangle burden, distinguishes AD from nondemented aging. To examine this hypothesis, we compared these neuropathologic markers of AD in nondemented individuals and clinically defined subjects with AD (19).

The objectives were to 1) determine the utility of SPs (cored, neuritic, and total) and NFT densities in distinguishing nondemented aging (CDR = 0) from AD, uncomplicated by other potentially dementing disorders; and 2) validate the numeric criteria by deriving cut-points for SPs and NFTs that best discriminate nondemented controls and AD cases. The main outcome measures of the study were the sensitivity and specificity for each marker, considered separately and when their 3 neocortical scores were averaged, using receiver operating characteristic curves (ROCs) to discriminate between the AD and non-AD subjects.

MATERIALS AND METHODS

Subject Recruitment and Assessment

Subjects were enrolled in longitudinal research studies at Washington University’s Alzheimer’s Disease Research Center (ADRC) in St. Louis, Missouri. Recruitment and assessment procedures have been described in detail (12); recruitment is based on media appeals for both healthy and cognitively impaired individuals living in the community. All participants are assessed annually unless prevented by death, refusal, or relocation far from St. Louis. All procedures are approved by the Washington University Human Studies Committee.

The inclusionary and exclusionary clinical criteria for AD used in this study have been validated (10). The gradual onset and progression of impairment in memory and other cognitive domains is required for diagnosis, comparable to the “probable AD” category reported by the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer Disease and Related Disorders Association (19). Other known neurologic, psychiatric, or medical illnesses that are considered to have the potential to be the primary cause of dementia are excluded at enrollment. Diagnostic accuracy of our clinical criteria for AD is 93% (12). Nondemented subjects lack known causes of dementia and have no cognitive or functional impairment.

Determination of nondemented or AD status is based on clinical methods. Experienced neurologists, psychiatrists, geriatricians, and nurse clinicians conduct semi-structured interviews with the subject and a collateral source who knows the subject well. A neurologic examination of the subject is also conducted. The assessment protocol contains items from standard brief cognitive batteries, including the Mini-Mental State Examination (MMSE) (20) and the Short Blessed test (21). The presence of dementia and, when present, its severity, is staged with the Clinical Dementia Rating (CDR) (22). The CDR rates cognitive function along 5 levels of impairment from none to maximal (0, 0.5, 1, 2, or 3) in each of 6 domains: memory, orientation, judgment and problem solving, function in the community, function at home, and personal care. Only impairment caused by cognitive dysfunction is rated. The global CDR score is derived from the individual ratings in each domain such that CDR 0 indicates no dementia and CDR 0.5, 1, 2, or 3 indicate very mild, mild, moderate, or severe dementia. Interrater reliability for the CDR is established (23, 24). A separate 1.5-hour psychometric battery is administered to all subjects at each assessment as described in detail elsewhere (25).

In all subjects who are autopsied, a validated retrospective postmortem interview is conducted with the collateral source to assess the cognitive status of the subject from time of last assessment until death (26). Before the autopsy results are known, a senior clinicianreviews all clinical assessments and the postmortem interview and generates an Expiration Summary. This Summary yields a final CDR and dementia diagnosis for the subject.

The sample studied here was comprised of individuals in our longitudinal cohort who came to autopsy from January 1981 through May 1996 and who were not members of a kindred with a known causative mutation for AD. This was the same set of cases reported by Berg et al (12). Additional criteria for the sample included 1) full morphometric data, 2) last clinical assessment within 2 years of death, 3) a nondemented or an AD diagnosis, and 4) no other potentially dementing diagnosis. One hundred fifty-seven individuals had full morphometric data. We deliberately undersampled those who were at CDR level 3 at time of death. Of these, 25 were excluded because their final clinical assessment was more than 2 years prior to death. Nine were excluded for nonstandard assessment. Of the others, 8 had questionable AD diagnoses and 73 had some other potentially dementing diagnoses. The remaining 42 individuals served as the sample for this study.

The validity study of the cut-points derived from these 42 individuals was applied to the 149 subjects obtained from the 157 subjects with full morphometric data after excluding 8 patients who were either given non-AD diagnoses at expiration (clinical diagnoses) or were missing expiration diagnoses. The pathologic diagnoses assigned to these individuals (85 women, age range 43.4 to 106.2 years; 64 men, age range 50.5 to 95.7 years) is presented in Table 5.

Neuropathology

The methods used for quantifying AD brain lesions have been described in detail in previous publications (11–13), and will be described here only briefly.

Lesion counts were made on 5 brain regions defined initially by CERAD (5), where region 1 = middle frontal gyrus; region 2 = superior temporal gyrus; region 3 = inferior parietal lobule cortex; region 5A = hippocampal subfield CA1; region 5B = entorhinal cortex at the level of the lateral geniculate body. Total (TSP) and cored (CSP) senile plaques were assessed quantitatively using a modification of the Hedreen-Bielchowsky silver method (13). Neuritic pathology (i.e. neuritic senile plaques [NSPs] and extracellular and intraneuronal NFTs) was also assessed using this modified method. Both intracellular and extracellular tangles were included in the NFT counts. Total SPs included all varieties of argyrophilic diffuse and neuritic plaques.
plaques. Diffuse plaques are amorphous or finely fibrillar deposits and lack abnormal argyrophilic neurites or central cores. Neuritic plaques contained abnormal swollen argyrophilic neurites. CSPs were a subset of neuritic plaques and contained central compact cores. Neuritic plaque densities were determined by means of one silver method on a section on frontal cortex within 50 μm of the section used for TSP densities with the other silver method (13).

NSPs were visualized using the modified Bielschowsky silver method. To be counted as neuritic a plaque had to contain within its boundaries one or more distended, abnormally configured neuritic process, whether or not a central core was present. Many NSPs did not have such a central core in a given plane of section.

NFTs were identified if the classical tangle configuration was evident. Two types of tangles were included in this lesion category: 1) classical NFT corresponding to argyrophilic, compact, and fascicular intraneuronal fibrillary structures that were thicker than neurofilaments; or 2) extracellular NFTs with no associated nuclear or cytoplasmic structures that were composed of fibrillar, loose structures that stained more faintly (tan or light brown) with silver than did the blacker intraneuronal tangles. Extracellular NFTs were identified in the neuropil primarily in regions 5A and 5B, where conversion of intraneuronal to ghost tangles has been well documented.

SP counts were done using a ×10 objective and a 1 × 1 cm² reticule with 100 subdivisions. Actual field size was calibrated using a microscope stage micrometer. Ten contiguous nonoverlapping microscopic fields were counted for each marker (Fig. 1). Five fields were from the upper cortex bordering the pial surface and 5 fields were from the lower cortex bordering the grey-white matter intersection. SP counts proceeded from the depth of a gyrus towards the gyral crest. Conversely, NFT density counts proceeded from the gyral crest towards the trough. The geometric mean of these 10 field densities was computed to represent the average density. This methodology provides a measure of average lesion density for ten 1-mm² microscopic fields. A total of 10 mm² thus was assessed for each individual anatomic region and 30 mm² was assessed for the neocortical composite. A combined plaque score derived from averaged density counts of the 3 neocortical regions was used.

A modified counting paradigm was used to count region 5A hippocampal CA1 total and cored neuritic plaques and NFTs. Lesions were counted in ten 1-mm² microscopic fields proceeding from the medial CA2/CA1 junction of the pyramidal layer laterally towards the subiculum. An average of the 10 field counts was then computed as above. This counting method provided coverage of the entire medial to lateral extent of CA1. Region 5A and 5B counts from the ten 1-mm² microscopic fields assessed were combined to form a hippocampal composite score for each type of lesions assessed (TSP, CSP, NFT).

The reliability of identifying TSPs (Hedreen-Bielschowsky silver method) and NFTs (modified Bielschowsky silver method) was done by blindly recounting (DWM) these markers in
25 cases. The Pearson correlation coefficients showed reasonable agreement for the independently made sets of counts: r = 0.95 for TSPs and r = 0.82 for NFTs.

Washington University Neuropathologic Criteria for AD

The quantitative neuropathologic criteria used to diagnose AD are derived from National Institute of Aging consensus criteria (4) and thus utilize both neocortical SPs and NFTs. The average TSP density (number per mm²) of ten 1-mm² microscopic fields in 6-μm-thick paraffin sections must exceed in at least 1 standard neocortical region (midfrontal, superior temporal, inferior parietal) the following age-adjusted plaque scores: less than 50 years, 2 to 5/mm²; 50 to 65 years, 8/mm² or more; 66 to 74 years, 10/mm² or more; 75 years or greater, 15/mm² or more. At least some neocortical NFTs must be present at all ages. Brains from individuals with a CDR of 0.5 at death or greater with TSP densities that exceed these criteria are classified as having neuropathologic AD; brains that fail to meet these criteria are diagnosed as “no AD.”

Statistical Analysis

The distribution of plaque and tangle densities in the 10 fields for each of the 5 regions shows substantial variability and is skewed to the right. The statistical analysis is done on the transformed density variable for each subject obtained by first taking the logarithm of each field density (adding 0.05 to each density to avoid logarithm of 0) and then taking the average of these logarithms. Values have been transformed back to the original scale (counts/mm²) for clarity in presentation.

Since the sensitivity and specificity of a diagnostic test with a continuous scale of values depends on the specific cutoff point selected, we chose the ROC curve approach for each neuropathologic marker (27–29) in relation with the neuropathologic diagnosis. The ROC curve is computed by calculating the sensitivity and specificity for each possible cut-point in the distribution. A common statistic to summarize the diagnostic accuracy of a measure is the area under the curve (AUC). An AUC of 1.0 reflects perfect discrimination, whereas an AUC of 0.5 reflects only a chance association of a measure with the diagnosis. We computed the AUC (and its 95% confidence interval) for each neuropathologic marker for each of the anatomic locations.

To better compare criteria across markers and anatomic locations, we calculated a smoothed ROC by fitting the binormal form using the ROCKIT computer program written by Metz (ROCKIT 0.9B, Beta version, available from Charles E. Metz, Department of Radiology, University of Chicago). We calculated the estimated sensitivity (and its 95% confidence interval) for a fixed specificity of 90%. The corresponding cut-point to achieve such sensitivity and specificity was also calculated based on the estimated binormal ROC curves and the inverse of the standard normal distribution function. The complete set of subjects with the same neuropathologic markers quantified was then used to assess the degree to which the cut-off scores performed in a more heterogeneous collection of cases (12).

RESULTS

Table 1 lists the demographic features of the study sample. The mean ± SD age at death of all 35 demented
Fig. 2. Standard receiver operating characteristic (ROC) curves are shown in the left panels (A, C, E) and corresponding lesion density scatter plots are shown in the right panels (B, D, F). A: ROC for total neocortical plaques in region 1 (midfrontal cortex). B: Lesion density scatter plot for total neocortical plaques in region 1 (midfrontal cortex). C: ROC for total neocortical tangles in region 3 (inferior parietal cortex). D: Lesion density scatter plot for total neocortical tangles in region 3 (inferior parietal cortex). E: ROC for total tangles in region 5B (entorhinal cortex). F: Lesion density scatter plot for total tangles in region 5B (entorhinal cortex).

### Table 2

Area under the Curve (AUC) by Anatomic Location for NFTs and SPs

<table>
<thead>
<tr>
<th>Anatomic location</th>
<th>Tangles</th>
<th>Total plaques</th>
<th>Cored plaques</th>
<th>Neuritic plaques</th>
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<tbody>
<tr>
<td>NEOCORTEX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region 1: dorsolateral middle frontal gyrus (A9/46)</td>
<td>0.876 ± 0.104</td>
<td>0.969 ± 0.028</td>
<td>0.971 ± 0.025</td>
<td>0.950 ± 0.033</td>
</tr>
<tr>
<td>Region 2: superior temporal gyrus (A22)</td>
<td>0.925 ± 0.042</td>
<td>0.970 ± 0.026</td>
<td>0.973 ± 0.024</td>
<td>—</td>
</tr>
<tr>
<td>Region 3: inferior parietal lobule (A39)</td>
<td>0.804 ± 0.073</td>
<td>0.982 ± 0.020</td>
<td>0.910 ± 0.060</td>
<td>—</td>
</tr>
<tr>
<td>Average of Regions 1, 2, 3</td>
<td>0.912 ± 0.071</td>
<td>0.986 ± 0.018</td>
<td>0.970 ± 0.027</td>
<td>—</td>
</tr>
<tr>
<td>HIPPOCAMPAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5A: hippocampal CA1 (A28)</td>
<td>0.836 ± 0.102</td>
<td>0.972 ± 0.024</td>
<td>0.833 ± 0.078</td>
<td>—</td>
</tr>
<tr>
<td>5B: entorhinal cortex (A28)</td>
<td>0.658 ± 0.139</td>
<td>0.962 ± 0.029</td>
<td>0.934 ± 0.067</td>
<td>—</td>
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</table>

Subjects (80.4 ± 10.5, range 43–105 years) was not different from that of the 7 control subjects (80.9 ± 7.1, range 70–89 years). The CDR 0.5 and 2 groups were slightly older than the CDR 3 group (p < 0.02). Scores on the Short Blessed test increased with dementia severity, as expected (too few subjects completed the MMSE, which was implemented in 1996, to report). There were no significant differences among the CDR groups for amount of education or the interval from the last clinical assessment to death. On average, subjects were last examined clinically within 12 months from the time they died.

**ROC Curve Analysis**

Examples of ROC curves are shown in Figure 2. Figure 2A shows data for TSPs in neocortical region 1 and Figure 2B shows a scatter plot for the same data. Since 1 AD subject had a count of 0, the maximum sensitivity is 0.97 (34/35). This same sensitivity is maintained for counts up to 3.5 while the specificity increases to 0.86 (6/7) as 6 of the 7 controls had counts less than 3.5. With a cut-point of 15.1, all of the controls would be correctly classified, but the number of AD subjects correctly classified would drop to 0.94 (33/35).

Figure 2C and 2D show similar plots for NFTs in neocortical region 3. Because of the large number of cases with AD who have counts near 0, using a cut-point of between 0 and 0.058 results in a sensitivity of 0.71 (24/34) with a specificity of 0.72 (5/7). Raising the cut-point to between 0.058 and 0.1 increases the specificity to 1.0, but drops the sensitivity to 0.65 (22/34). Figure 2E and 2F show the plots for NFTs in hippocampal region 5b where there is essentially no relationship between the lesion count and the diagnosis.

Table 2 shows the AUC and the corresponding standard error for each of the 3 markers for the anatomical areas. The AUCs for all types of SP measures are very high, approaching 1.0. For example, in frontal cortex TSPs, CSPs, and NSPs fall between the AUC range of 0.950 and 0.971. AUCs for TSPs and CSPs are almost identical in frontal and temporal cortex, whereas TSPs have slightly higher AUCs compared to CSPs in the other
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TABLE 3

<table>
<thead>
<tr>
<th>Anatomic location</th>
<th>Estimated Sensitivity for 90% Specificity</th>
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<tbody>
<tr>
<td></td>
<td>Estimated sensitivity (%), (range)</td>
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<tr>
<td></td>
<td>Cut-point No./mm²</td>
</tr>
<tr>
<td>Tangles</td>
<td>Sensitivity</td>
</tr>
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<td></td>
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<tr>
<td>NEOCORTEX</td>
<td></td>
</tr>
<tr>
<td>Region 1: dorsolateral middle frontal gyrus (A9/46)</td>
<td>66.9, (27.6±92.9)</td>
</tr>
<tr>
<td>Region 2: superior temporal gyrus (A22)</td>
<td>79.9, (52.5±85.8)</td>
</tr>
<tr>
<td>Region 3: inferior parietal lobe (A39)</td>
<td>63.3, (35.2±85.8)</td>
</tr>
<tr>
<td>Averaged over Regions 1, 2, 3</td>
<td>79.9, (52.5±85.8)</td>
</tr>
<tr>
<td>HIPPOCAMPUS</td>
<td>5A: hippocampal CA1 (A26)</td>
</tr>
<tr>
<td></td>
<td>5B: entorhinal cortex (A28)</td>
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<td></td>
<td>5B: entorhinal cortex (A28)</td>
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</table>

Diagnostic Sensitivity and Specificity

The estimated sensitivity along with a 95% confidence interval for quantitative lesion counts to achieve a specificity of 99.0% is shown in Table 3. Quantitative lesion density counts to achieve the estimated sensitivity and 90% diagnostic specificity are also given in Table 3.

Using a combined cutoff score of 6.0 TSPs per mm² of (frontal and parietal) neocortex confers a 97.8% sensitivity for a 90% specificity for establishing a criterion-based quantitative neuropathologic diagnosis of AD. Quantifying NFTs and using a cut-point of 0.7 in the same 3 neocortical regions provides only 83.3% sensitivity for the same 90% specificity.

Tables 2 and 3 show that across all 5 regions, TSPs provide greater estimated AUC and diagnostic sensitivity at a fixed 90% specificity than do NFTs.

Validity Testing of Cutoff Score Based on Washington University ADRC Diagnostic Criteria for AD

A major purpose of this analysis was to establish the validity of plaque and tangle cutoff values for diagnosing AD (Table 3). Table 4 shows the observed sensitivity and specificity when applied to the validity sample of 149 subjects. This heterogeneous group represents the case mix seen among those seen by our center and who died with either a clinical diagnosis of AD, or as not demented, regardless of their neuropathologic diagnosis.

Data in Table 5 shows that of the 149 test cases, 11 were not demented and 138 were demented. Definite (NIA-Reagan high probability) AD was the sole diagnosis in 85 brains while 27 brains had AD pathology mixed with another secondary dementing disorder. Ten additional cases had intermediate and low probability AD. Fourteen cases had either pure or mixed Parkinson disease (n = 2), the Lewy variant of AD (n = 11), or dementia with Lewy bodies (DBL) (n = 1) as the sole dementing diagnosis. Only 1 case had primary vascular dementia and 1 case had dementia lacking distinctive histopathologic features.

This type of data analysis validates the utility of the cutoff score and the Washington University ADRC quantitative criteria. The discriminant analysis requirement that both “training” and “test” data sets are used is also satisfied.

DISCUSSION

The data presented strongly suggest that densities of total neocortical SPs (neuritic plaques and diffuse plaques) provide very high specificity and estimated sensitivity for the diagnosis of AD. Neither neocortical nor hippocampal NFTs discriminated nearly as well between the nondemented and demented AD groups based on the

3 regions. TSP AUCs are higher compared to AUCs for NFT across all 5 sampled brain regions.

Estimating sensitivity and 95% confidence interval as calculated from the binormal ROC model.
estimated AUC and sensitivity with a fixed specificity of 90%. Cutoff scores of 7.9 SPs/mm² in mid-frontal neocortex (Brodmann area 9/46), 8.5 SPs/mm² in superior temporal neocortex (Brodmann area 22), and 5.2 SPs/mm² in inferior parietal lobule neocortex (Brodmann area 39/40) will confer 90% specificity and 94% to 98% sensitivity for diagnosing AD. These plaque densities lie within the range of SP densities diagnostic of AD for persons 50 to 75 years old at death as recommended in the original NIA consensus criteria (4). The age-adjusted neocortical plaque density threshold for persons 75 years or older was 15/mm². Average neocortical plaque densities decline modestly rather than increase as a function of age (12); thus, our cutoff scores should apply to the diagnosis of AD regardless of age.

We used brain sections from carefully screened, longitudinally assessed research subjects who were clinically diagnosed as either CDR 0 demented or CDR 0.5 to 3 AD groups. The present results indicate that diffuse plaques, which have been shown repeatedly to dominate the neocortical landscape early in the course of very mild AD (12, 13, 16–18, 30), have great diagnostic import and should not be ignored.

The identified cutoff values shown in Table 3 were also consistent with previously formulated Washington University quantitative criteria (11–13) for diagnosis of AD. These criteria are a modification of the 1985 NIA consensus criteria (4). The main modifications are 1) a modified Bielschowsky silver stain that better visualizes the whole range of senile plaques, including the diffuse variety (31); and 2) a counting protocol that evaluates the total number of SPs in 10 contiguous 1 mm² microscopic fields in each brain region. This strategy was designed to assess total average plaque distribution across a 10 square millimeter expense of cortex, thus precluding a diagnosis of AD based on only 1 to 3 selected fields. Our counting protocol differs from the 1985 NIA consensus quantitative method whereby SP density in only a single microscopic field has to meet or exceed criteria, and from the CERAD semiquantitative counting strategy in which only NSPs are evaluated and maximal plaque counts in any 3 microscopic fields are averaged and compared to cartoons that depict mild, moderate, and severe plaque numbers for 1 field. The recently proposed NIA-Reagan Institute diagnostic criteria for AD incorporates the CERAD SP assessment method (6).

We find that neocortical SPs constitute the best marker to differentiate AD, even at the earliest symptomatic stage (CDR 0.5), from nondemented controls (11–13, 15). Neocortical SPs do correlate moderately (r = 0.4 to 0.5) with dementia severity as staged by the CDR, albeit not as robustly as neocortical NFTs. These findings are supported by findings of other investigators who also employed silver methods to detect SP (32). However, data from many centers, including our own (12),

<table>
<thead>
<tr>
<th>Anatomic location</th>
<th>Tangles</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Neocortical plaques</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Cored plaques</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Neuritic plaques</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
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</table>
show that neocortical tangle density correlates more robustly than plaque density with measures of dementia severity (33).

Hippocampal and entorhinal allocortical and transition- al cortical SPs also may discriminate CDR 0 subjects from those with cognitive impairment even at the very mild Alzheimer-type dementia (DAT) stage, but this effect is less robust than for neocortical CSPs and TSPs (12).

It is now generally accepted that at least a few hippocampal CA1 and entorhinal cortex layer II (ERC-II) NFTs occur in the brains of nondemented persons, perhaps beginning around age 50. Hippocampal and ERC-II NFT densities increase during the course of AD. We find that CA1 NFTs have a somewhat more discriminant value between cognitive normality (CDR 0) and AD primarily because ERC-II stellate neurons develop pretangles and tangles earlier than do hippocampal CA1 pyramidal neurons (7). Significant entorhinal layer II neuron loss also occurs very early in CDR 0.5 AD (18). Perhaps because of their early accumulation, ERC-II tangles correlate only weakly with CDR although they build up progressively in that location. One difficulty in assessing the natural history of ERC-II and CA1 NFTs in AD is their propensity to truncation by proteolytic digestion accompanied by loss of argyrophilia and PHF tau labeling of antibodies directed at the protease-susceptible N- and C-termini (34). These extracellular “ghost” tangles may be more difficult to count than intraneuronal NFTs, which label robustly with many silver methods and PHF tau directed antibodies. Berg et al have shown that neocortical NFTs occur at very low densities in neocortex of CDR 0.5 AD subjects to the extent that such cases form a significant proportion of our “plaque predominant” or “plaque only” AD (12).

Our results underscore the clearcut histopathologic differences in plaque and tangle markers between normal aging, as represented by the marker profile of the nondemented (CDR 0) control group, and the AD-equivalent marker profile of the very mild AD (CDR 0.5) group. The marker densities for the very mild DAT group confirm that individuals at the CDR 0.5 stage in this sample have AD. The present data reinforce and strengthen the conclusions reached by Morris et al in 1996 (16) and by Price and Morris in 1999 (18) who proposed that a subset of nondemented persons whose brains harbored numerous and widespread neocortical plaques (superimposed on aging-related hippocampal tangles) had “preclinical” AD. The preclinical case histopathologic marker profile was almost identical to that of the CDR 0.5 very mild AD group.

The present findings must also be viewed in light of new and emerging diagnostic criteria for diagnosing AD histopathologically such as the 1997 NIA-Reagan Institute has proposed (6, 35, 36). This important development has emphasized a probabilistic approach (low, intermediate, and high likelihood) to AD diagnosis that emphasizes the importance of SPs and NFTs being pathologic lesions. The new diagnostic criteria also emphasize using neurofibrillary pathology according to the hierarchical model described by Braak and Braak in 1991.

<table>
<thead>
<tr>
<th>Neuropathologic diagnoses (primary and secondary dementing disorders)</th>
<th>Number of brains with pathology</th>
<th>Percent of total brains (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal brain, no pathology</td>
<td>7</td>
<td>4.7%</td>
</tr>
<tr>
<td>No primary, stroke not VaD secondary</td>
<td>4</td>
<td>2.7%</td>
</tr>
<tr>
<td>Pure AD definite (NIA-Reagan high probability)</td>
<td>85</td>
<td>57.0%</td>
</tr>
<tr>
<td>Mixed AD definite (NIA-R high probability):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. AD definite/high, incidental Lewy pathology</td>
<td>2 (1.3%)2</td>
<td></td>
</tr>
<tr>
<td>2. AD definite/high, hippocampal sclerosis</td>
<td>3 (2.0%)2</td>
<td></td>
</tr>
<tr>
<td>3. AD definite, progressive supranuclear palsy</td>
<td>1 (0.7%)2</td>
<td></td>
</tr>
<tr>
<td>4. AD definite, Other (not otherwise specified)</td>
<td>2 (1.3%)2</td>
<td></td>
</tr>
<tr>
<td>5. AD definite, stroke not VaD1</td>
<td>18 (12.1%)2</td>
<td></td>
</tr>
<tr>
<td>6. AD definite, secondary unknown</td>
<td>1 (0.7%)2</td>
<td></td>
</tr>
<tr>
<td>Pure Parkinson disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Parkinson’s, mixed with stroke not VaD</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Pure AD Lewy body variant (AD-LBV)</td>
<td>5</td>
<td>3.5%</td>
</tr>
<tr>
<td>Mixed AD-LBV with stroke not VaD</td>
<td>5</td>
<td>3.5%</td>
</tr>
<tr>
<td>Mixed AD-LBV with Other (not specified)</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Dementia with Lewy bodies (DLB), no AD pure</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Vascular dementia (VaD) primary</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>No primary diagnosis, stroke not VaD</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Total cases</td>
<td>149</td>
<td>100%</td>
</tr>
</tbody>
</table>

1 VaD = vascular dementia.
2 Percentages in parentheses are subcategories under “Mixed AD definite (NIA-R high probability)” main category.
(7). Use of these criteria, however, would result in many of CDR 0.5 and some CDR 1 cases being classified as “low probability” AD despite convincing clinical and psychometric data that indicate that they have recognizable progressive dementia, distinct from cognitive changes associated with non-demented aging (37). This suggests that NFT-based neuropathologic criteria will be weighted toward diagnosing AD in its moderate and severe stages, because neocortical neurofibrillary pathology—although present—is relatively modest in early-stage AD (i.e. very mild and mild DAT).

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REFERENCES


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