Vascular Dementia in a Population-Based Autopsy Study

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Background: The validity of the clinical diagnosis of vascular dementia (VaD) remains suboptimal.

Objective: To investigate clinicopathologic correlations in VaD.

Methods: We used the medical records-linkage system of the Rochester Epidemiology Project to identify incident cases of dementia in Rochester, Minn, from January 1, 1985, through December 31, 1989. Dementia and Alzheimer disease (AD) were defined by the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Vascular dementia was defined by criteria including imaging results. Pathological characteristics of AD were quantified by means of standard scoring methods for neurofibrillary tangles and neuritic plaques. Vascular pathological findings were assessed by expert neuropathological opinion.

Results: Of 419 patients with dementia who died before the study, neuropathological examination results were available in 89 (21%) with median age at onset of 80 years (range, 50-96 years; 52 [58%] women). Pathological diagnoses were AD in 45 patients (51%), pure VaD in 12 (13%), combined AD and VaD in 11 (12%), and other diagnoses in the remaining 21 patients. Criteria for VaD that required either a temporal relationship between a stroke and dementia onset or worsening, or bilateral infarctions in specified locations demonstrated on imaging results (Mayo Clinic criteria) had 75% sensitivity and 81% specificity for pure VaD (positive likelihood ratio, 3.9; 95% confidence interval, 2.2-6.7). Five cases of pure VaD lacked the temporal relationship and accounted for the imperfect sensitivity of the criteria.

Conclusions: In this population-based autopsy study, the presence of vascular pathological characteristics in the absence of major AD pathological findings was common. Pure VaD without overt clinical strokes remains a challenge for antemortem diagnosis.

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The contribution of vascular pathologic characteristics to dementia is complex and remains unclear. This is reflected in the poor validity of clinical diagnostic criteria when compared with postmortem diagnoses.1-7 However, the interpretation of clinicopathologic studies has been hampered by different sources of patients across studies. For example, the frequency of vascular dementia (VaD) in autopsy series was much higher when recruitment was from well-defined populations1,8 compared with dementia clinics.5,9 The relative rarity of prospective studies of patients with dementia who prove to have VaD neuropathologically limits our ability to improve clinical diagnostic criteria.

Our study of dementia from 1985 through 1989 in Rochester, Minn, allowed us to describe the incidence, survival,11 and clinicopathologic correlation (present study) of VaD. The unique access to clinical data on dementia and stroke in a geographically defined population, together with autopsy results on 21% of incident cases of dementia, enabled us to study the relationships between clinical features and neuropathological diagnoses.

METHODS

CASE ASCERTAINMENT AND CLINICAL DIAGNOSIS

We used the medical records-linkage system of the Rochester Epidemiology Project to identify all subjects residing in Rochester who developed dementia during the 5-year period from January 1, 1985, through December 31, 1989. Details about the study population and the identification of incident cases were reported elsewhere.10,12,13 Age- and sex-specific incidence rates for dementia, AD, and VaD in the Rochester population were reported previously.10,12 To be
included in the study, patients with dementia were required to have resided in Rochester in the year of onset of dementia and for at least 1 preceding year. Patients who had moved to Rochester for the management of a preexisting dementing illness were excluded. A series of nondemented referent subjects from the same population was also identified through the records-linkage system; however, because the referent subjects were not followed up prospectively, their dementia status at the time of death was unknown. Therefore, these referent subjects could not serve as controls for neuropathological studies.

Information for the diagnosis of dementia and for the classification of cases by type of dementia was abstracted from the medical history, neurological examinations results, and neuro-imaging study findings as collected historically in the patient documents of the records-linkage system. Diagnostic criteria for dementia and for Alzheimer disease (AD) were those of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). On the basis of our previous work, we defined VaD as either (1) dementia onset or worsening within 3 months of clinical stroke or (2) bilateral gray matter infarctions shown by imaging that fulfilled specified location criteria (critical imaging lesions). We refer to these as the Mayo Clinic criteria. We also independently applied the following 4 sets of published diagnostic criteria for VaD: the DSM-IV criteria, the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) probable VaD criteria, the International Classification of Diseases and Related Health Problems, 10th Revision of the World Health Organization (ICD-10) criteria, and the State of California Alzheimer’s Disease Diagnostic and Treatment Centers (ADDTC) criteria. Imaging findings were only used for the classification of dementia if they were obtained from 1 year before through 3 years after the onset of dementia. We excluded imaging lesions that clearly postdated the onset or the early phase of dementia.

### AUTOPSY AND PATHOLOGICAL DIAGNOSIS

Patients from our incidence series who died before the time of this study underwent autopsy according to routine clinical practice. No special brain donation program was available for dementia in the study population at the time of this study. Pathological samples pertaining to residents of Rochester are routinely archived and are retrievable for additional studies.

Neuropathological examinations were carried out under the supervision of one of 2 board-certified neuropathologists (J.E.P. and Haruo Okazaki, MD). Written records of the original neuropathological examination were reviewed for descriptions of gross pathologic findings. These records often contained reference to clinical information such as a history of stroke; therefore, our pathological diagnoses cannot be considered independent of clinical information. For the cases that underwent autopsy in the late 1980s and early 1990s, the original routine neuropathological examinations included only hematoxylin-eosin staining plus Bielschowsky silver staining. Brain regions sampled included frontal, temporal, parietal, and occipital neocortices, and striatum, hippocampus, amygdala, midbrain,pons, and medulla. Because the brains were acquired in the context of routine clinical activities, there was no additional standardization for location of the tissue samples within a particular region or for thickness of the slices. Both hemispheres were available for gross and microscopic inspection. At later dates, some cases also underwent tau or β-amyloid immunostaining. All pertinent histopathological reports, photographs of gross specimens, and histologic sections were first examined by three of us (J.E.P. and A.S. [2 neuropathologists] and H.A. [a neurologist]), then they were all reviewed by a dementia expert (D.K.). All cases with vascular or uncertain pathological features were reexamined by the primary study neuropathologist (J.E.P.), and, if necessary, additional slides were made using tau, β-amyloid, or α-synuclein immunohistochemical techniques.

The pathological diagnosis of AD was made using a combination of the criteria of the Consortium to Establish a Registry for AD (CERAD) (based on the count and location of neuritic plaques) and the staging system of Braak and Braak (based on the count and location of neurofibrillary tangles). The pathological diagnosis of AD was made when either a brain met CERAD probable or definite AD criteria or the Braak and Braak stage was IV or higher.

The neuropathological diagnosis of VaD was made if there were multiple infarctions in gray matter structures from the thalamus rostrally. Frank infarctions in white matter were also included. Bilaterality of infarctions, but not necessarily in the same structures, was required. Neurofibrillary tangles that were less than or equal to Braak and Braak stage III and neuritic plaques that were considered sparse or less by CERAD criteria were required for a diagnosis of pure VaD. In addition, the absence of other pathological characteristics was required for a diagnosis of VaD. When other pathological features were present in the setting of substantial vascular pathological findings, multiple diagnoses were made (eg, the combination of VaD and AD). The diagnosis of dementia with Lewy bodies was based on Lewy body pathological changes in the substantia nigra, amygdala, and neocortex.

### STATISTICAL METHODS

The χ² and rank sum tests were used to compare cases with and without autopsy results, and to compare groups with different pathological diagnoses. Sensitivity, specificity, positive predictive value, negative predictive value, and positive likelihood ratio (with 95% confidence interval) were calculated to compare clinical features or clinical diagnoses with pathological diagnoses (standard for comparison). Only cases of dementia were included in the calculations of diagnostic accuracy; the study did not involve a group of controls (subjects who died without dementia).

### RESULTS

There were 482 incident cases of dementia identified in Rochester from January 1, 1985, through December 31, 1989. Eighteen percent of these were diagnosed as having VaD by the Mayo Clinic criteria, and 4% were diagnosed as having probable VaD by the NINDS-AIREN criteria. Of the 419 incident patients with dementia who were deceased at the time of this study, neuropathological examination results were available in 89 cases (21% of all deceased; 52 [38%] women). At onset of dementia, 9 of the autopsied cases were younger than 70 years, 7 were 70 years and older, and the remaining 73 were between 70 and 90 years.

We compared patients with dementia who underwent autopsy with those who died but did not undergo autopsy. Autopsied patients were younger at onset of dementia (median age, 80 years; range, 50-96 years) compared with those who died and were not autopsied (median age, 84 years; range, 52-100 years; P = .004, rank sum test). Patients with a temporal relationship between dementia and stroke underwent autopsy more frequently than did others (15 [17%] vs 35 [11%]); however, the difference was not statistically significant. The autopsied patients had 2 or more strokes more often than did...
years; autopsied patients (median, 4 years; range, 1-13 years) had more than 1 small infarction (total infarct volume, <0.5 cm3).

The pathological diagnoses and demographic characteristics of the 89 patients are given in Table 1. There were 45 patients (51%) in whom AD was considered the sole cause of the dementia and 9 (10%) with Lewy body disease. Twelve patients (13%) had pure VaD and 11 (12%) had combined VaD and AD. The diagnoses of the remaining patients are described in Table 1. The distribution by temporal relationship between dementia and stroke and by presence of critical infarctions on imaging is also given in Table 1. Both these clinical features of vascular disease were infrequent in autopsy-proved AD and in patients having dementia with Lewy bodies. By contrast, both vascular features were common among those with pure VaD or the combination of VaD and AD.

Details about the pathological findings of the patients with pure VaD and those with combined VaD and AD are given in Table 2. The data in Table 2 allow the reader to observe the effects of varying the diagnostic cut points for AD and VaD. Of the 12 patients with pure VaD, 7 had large vessel–distribution infarctions with or without additional lacunar infarctions, 4 had exclusively lacunar infarctions, and 1 had predominant leukoencephalopathy. In the 45 patients diagnosed as having pure AD and the 9 with Lewy body disease, some cerebrovascular disease was present: 15 (17% of the 89 who underwent autopsy) had at least 1 microscopic or small infarction in the thalamus or more rostrally. Four of the 15 patients had more than 1 small infarction (total infarct volume, <0.5 cm3).

Table 3 shows the sensitivity, specificity, and positive likelihood ratio for individual features and for several sets of diagnostic criteria in the patients with pure VaD and in those with pure VaD or VaD and AD. For patients with pure VaD, the Mayo Clinic criteria were modestly sensitive and specific; the ICD-10 criteria and the DSM-IV criteria (including white matter lesions) had similar sensitivity but lower specificity than the Mayo Clinic criteria, and the NINDS-AIREN criteria (including or excluding white matter lesions) were less sensitive but more specific. The ADDTC criteria were less sensitive than the Mayo Clinic criteria but equally specific. For pure VaD and combined VaD and AD together, the Mayo Clinic criteria were less sensitive but more specific than the ICD-10 and the DSM-IV criteria (including white matter lesions). The positive predictive value of the Mayo Clinic criteria for pure VaD and combined VaD and AD was 63% and the negative predictive value, 88%.

The imperfect sensitivity of the diagnostic criteria for pure VaD was due to 5 patients with pure VaD at neuropathological examination who lacked a temporal relationship between a clinical stroke and the onset of their dementia. Rereview of the medical records of these 5 patients showed no evidence of stroke temporally related to dementia onset in 4, all of whom had family caregivers who were interviewed by behavioral neurologists. A major language barrier in the fifth case may have obscured the documentation of a stroke temporally related to the onset of dementia. Thus, 4 (33%) of 12 of our patients with pure VaD at pathological examination unequivocally lacked a temporal relationship between a clinical stroke event and their dementia. The patients with combined VaD and AD at pathological examination lacked a temporal relationship between dementia onset and stroke even more frequently (13 of 23 patients).

We also calculated the sensitivity and specificity of the DSM-IV diagnosis for AD in this cohort, excluding cases of combined VaD and AD (n = 45). The sensitivity was 98%, but the specificity was only 41%; the positive predictive value was 63%, with a negative predictive value of 95%.

**COMMENT**

The principal observations from our study were as follows: (1) Vascular dementia was common neuropatho-
The feature of dementia temporally related to stroke was the best clinical predictor of pure vascular pathological findings; however, this feature had imperfect sensitivity. (3) At least a few cases with pure VaD at neuropathological examination lacked a history of clinical stroke temporally related to the onset of dementia. In this population-based sample of incident cases of dementia who underwent routine pathological examination, VaD (or more precisely, etiologically relevant cerebrovascular disease) without AD, AD combined with VaD, and AD with small infarctions were common. The proportion of patients with dementia and etiologically important cerebral infarctions ranged from 13% to 25%. Despite the higher rate of autopsy for patients with clinical features of cerebrovascular disease that was observed in this study, and despite the imprecision of the clinical diagnosis of VaD, our estimates of the proportion of patients with VaD (those with pure VaD plus those with combined VaD and AD) are consistent with the results of our incidence study. We previously reported that the proportion of all incident cases of dementia classified clinically as VaD was 18% by the Mayo Clinic criteria. Our observed proportion of VaD at autopsy was also comparable to that from a population-based autopsy series from England. Patients with pure VaD constituted 11% of that series, and another 20% were patients with a combination of AD and VaD. 

One reason for our high proportion of VaD may be the population-based origin of our series. We were able to capture patients with stroke and subsequent dementia more completely than most other clinicopathologic studies. Patients with stroke who become demented may be less likely to be evaluated in dementia clinics and less likely to be given the diagnostic label of dementia. This may explain why VaD is less common in referral-based clinicopathologic series compared with population-based series. A second reason was the increased autopsy rate among cases with evidence of cerebrovascular disease. A third reason for our high rate of dementia attributed to VaD neuropathologically may be the presence of incidental cerebrovascular disease. The cerebrovascular disease observed in some patients with dementia may actually have been etiologically irrelevant. However, there is evidence against this hypothesis. We have studied the neuropathological findings of 39 elderly subjects who were evaluated cognitively within 1 year of death and found to be free of dementia at the Mayo Clinic Alzheimer's Disease Research Center, Rochester. None of these 39 nondemented subjects had a burden of chronic cerebral infarctions greater than that of the patients diagnosed as

<table>
<thead>
<tr>
<th>Sex/Age at Death, y</th>
<th>Plaque Pathological Findings by CERAD Criteria†</th>
<th>Braak and Braak Stage‡</th>
<th>Vascular Pathological Findings</th>
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<tbody>
<tr>
<td></td>
<td>Patients With Pure VaD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/95</td>
<td>None</td>
<td>II</td>
<td>4 Lacunar infarcts</td>
</tr>
<tr>
<td>M/65</td>
<td>None</td>
<td>I-II</td>
<td>5 Infarcts, including large L frontal, moderate R frontal</td>
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<tr>
<td>M/77</td>
<td>None</td>
<td>II</td>
<td>6 Lacunar infarcts</td>
</tr>
<tr>
<td>M/89</td>
<td>Sparse</td>
<td>II</td>
<td>4 Lacunar infarcts</td>
</tr>
<tr>
<td>M/87</td>
<td>None</td>
<td>II</td>
<td>4 Lacunar infarcts</td>
</tr>
<tr>
<td>M/77</td>
<td>None</td>
<td>II</td>
<td>&gt;6 Infarcts, including large R temporal</td>
</tr>
<tr>
<td>M/87</td>
<td>None</td>
<td>II</td>
<td>&gt;6 Infarcts, including moderate L frontal</td>
</tr>
<tr>
<td>M/69</td>
<td>None</td>
<td>II</td>
<td>&gt;6 Infarcts, including large R frontoparietal and L PCA</td>
</tr>
<tr>
<td>M/74</td>
<td>None</td>
<td>II</td>
<td>Multiple small cortical and deep infarcts plus moderate R PCA</td>
</tr>
<tr>
<td>F/90</td>
<td>Sparse</td>
<td>II</td>
<td>Extensive leukencephalopathy, 3 lacunar infarctions</td>
</tr>
<tr>
<td>F/86</td>
<td>Sparse</td>
<td>II</td>
<td>Moderate R PCA infarct</td>
</tr>
<tr>
<td>F/83</td>
<td>Sparse</td>
<td>II</td>
<td>5 Lacunar infarcts plus moderate L parietal</td>
</tr>
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<td></td>
<td>Patients With Combined VaD and AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/100</td>
<td>Sparse</td>
<td>IV</td>
<td>8 Infarcts, extensive leukencephalopathy</td>
</tr>
<tr>
<td>M/91</td>
<td>Sparse</td>
<td>IV</td>
<td>&gt;5 Infarcts</td>
</tr>
<tr>
<td>F/94</td>
<td>Sparse</td>
<td>III-IV</td>
<td>5 Large infarcts, including massive L MCA, large R PCA</td>
</tr>
<tr>
<td>F/93</td>
<td>Moderate</td>
<td>IV</td>
<td>2 Infarcts, including large L temporal</td>
</tr>
<tr>
<td>F/92</td>
<td>Sparse</td>
<td>IV</td>
<td>&gt;4 Lacunar infarcts</td>
</tr>
<tr>
<td>F/78</td>
<td>Frequent</td>
<td>IV</td>
<td>4 Infarcts, including large R parietal</td>
</tr>
<tr>
<td>F/67</td>
<td>Moderate</td>
<td>IV</td>
<td>3 Lacunar infarcts plus hippocampal infarct</td>
</tr>
<tr>
<td>F/89</td>
<td>Sparse</td>
<td>III-IV</td>
<td>&gt;6 Infarcts including several large cortical infarcts</td>
</tr>
<tr>
<td>M/86</td>
<td>None</td>
<td>V</td>
<td>2 Small infarcts</td>
</tr>
<tr>
<td>F/90</td>
<td>Moderate</td>
<td>V</td>
<td>3 Lacunes and vascular insult to CA1</td>
</tr>
<tr>
<td>M/82</td>
<td>Moderate</td>
<td>IV</td>
<td>2 Lacunar infarcts, including caudate and DM thalamus</td>
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Abbreviations: AD, Alzheimer disease; CA1, CA1 region of the hippocampus; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DM thalamus, medial dorsal nucleus of the thalamus; L, left; MCA, middle cerebral artery; NFTP, neurofibrillary tangle pathological findings; PCA, posterior cerebral artery; R, right; VaD, vascular dementia.

*Abundance of cored or neuritic neocortical plaques by the criteria of CERAD.
†From Braak and Braak. Stage I indicates NFTP confined to the transentorhinal cortex (layer IV); stage II, NFTP in entorhinal cortex (layer II); stage III, NFTP in hippocampus (CA1 and subiculum); stage IV, NFTP in association neocortex (mild); stage V, NFTP in association neocortex (moderate to severe); and stage VI, NFTP in primary cortices.
having pure AD in this study (D.K., J.E.P., B.F.B., R.H.C., A.S., Misericordia Floriach-Robert, MD, Robert Ivnik, PhD, Glenn Smith, PhD, Dennis Jackson, MD, Kris A. Johnson, Lindsay Petersen, William McDonald, Ronald Petersen, PhD, MD, unpublished data, 2002). In addition, the lack of other explanations for the dementia in our patients with pure VaD suggested that the observed cerebrovascular lesions were etiologically important. Empirical demonstrations that cerebrovascular disease worsens the expression of AD further suggest that cerebral infarction is relevant to the expression of late-life cognitive decline.24,25

Our results provided a disappointing but expected view regarding the diagnostic validity of clinical criteria

<table>
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<th>Table 3. Validity of Diagnostic Formulations for Pure VaD and for Broadly Defined VaD (Pure VaD Plus Combined VaD and AD)</th>
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<tr>
<td><strong>Diagnostic Criteria</strong></td>
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<tr>
<td>Temporal link between stroke and dementia Imaging findings strictly defined</td>
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<tr>
<td>VaD, Mayo Clinic criteria13</td>
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Abbreviations: AD, Alzheimer disease; ADDTC, criteria by the State of California Alzheimer’s Disease Diagnostic and Treatment Centers; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition; ICD-10, International Classification of Diseases and Related Health Problems, 10th Revision of the World Health Organization; n, numerator and denominator from which sensitivity or specificity is derived; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences; VaD, vascular dementia.

†For sensitivity, numerator indicates number of true positives; denominator, sum of true positives and false negatives. For specificity, numerator indicates number of true negatives; denominator, sum of true negatives and false positives.

‡Positive likelihood ratio is sensitivity divided by the result of 1 minus specificity.

§Onset or marked worsening of dementia within 3 months of a clinical stroke.

‖Bilateral gray matter infarctions shown by imaging in frontal, parietal, or temporal lobe cortex, thalamus; or basal ganglia.
for VaD. Similar findings have been reported by others. None of the criteria, including the Mayo Clinic criteria, had sufficient sensitivity to allow confident clinical detection of VaD. The specificity and negative predictive value of the criteria were much better for such detection. The feature of dementia that was temporally related to stroke had a high positive likelihood ratio. This feature is part of the NINDS-AIREN19 and ICD-10 criteria17; however, its contribution to sensitivity was severely reduced by the inclusion of other clinical features (such as focal neurological signs or imaging criteria) in the NINDS-AIREN criteria.

A new approach to the problem of imperfect sensitivity of VaD criteria is needed. Several patients with pathologically determined pure VaD and most of those with combined VaD and AD did not have clinical strokes that were temporally related to the onset of their dementia. The existence of these patients and our confidence in the absence of clinical strokes before the onset of dementia led us to conclude that there are 2 types of VaD. One type emerges from a clinical stroke event; the other develops in an insidious fashion without any clinically apparent stroke. The former type is readily diagnosed by the temporal profile of the dementia relative to clinical strokes and imaging findings of new infarctions. The latter type lacks a characteristic clinical profile but can be suspected on the basis of imaging study findings.

Several prospective imaging studies have demonstrated the occurrence of clinically silent infarctions. A gradually accumulating burden of infarctions or white matter ischemia could lead to a dementia that appears insidious and gradual. In addition, clinically silent cerebrovascular disease in the form of cerebral hypoperfusion could produce hippocampal neuronal loss or severe white matter pathological changes. We observed 1 case with ischemic leukoencephalopathy among the 4 patients without a clinical stroke. To improve the sensitivity of the diagnostic criteria for the insidious type of VaD will require better tools to distinguish nonspecific white matter lesions from severe ischemic leukoencephalopathy. The use of magnetic resonance imaging should increase the detection of lacunar infarctions that may be missed with computed tomography. Differentiation of ischemic vs AD pathologic changes in the hippocampus may also improve recognition of VaD. Finally, a reliable biomarker for AD would also be advantageous for VaD diagnosis.

Despite imperfect sensitivity in neuropathological terms, clinicians may find the Mayo Clinic criteria for VaD useful. The 2 features of dementia onset or worsening temporally related to a stroke and imaging evidence of bilateral gray matter infarctions are informative for predicting neuropathological findings, as demonstrated herein, and for predicting survival, as reported elsewhere. When both features are present (equivalent to the NINDS-AIREN criteria but ignoring the focal sign requirement), survival is decreased compared with those with neither feature, and the autopsy diagnosis is likely to be either pure VaD or combined VaD and AD. When only the temporal relationship feature is present, survival is nearly as poor, but the diagnostic likelihood of VaD at autopsy is slightly less. When only imaging evidence of critical infarctions is present in a patient with dementia, survival is only slightly worse than that for AD, and the neuropathologic findings are likely to include a substantial vascular component.

A strength of this study was the availability of an autopsy series derived from all incident cases of dementia in a defined population over a defined time interval. Clinical stroke is accurately detected by the medical record-linkage system serving our study population. Weaknesses of the study include the retrospective collection of clinical information, which may have led to a higher rate of identification of dementia in patients with strokes compared with those without strokes. In addition, because only a few patients underwent routine autopsy, our estimates of sensitivity and specificity may be biased. However, this limitation is common to any autopsy study. Indeed, the fact that we were able to characterize some of the differences between autopsied and nonautopsied cases was unique. Another weakness of our investigation was the lack of accepted and reliable pathological criteria for VaD; it is possible that we underdiagnosed pure VaD as a result of our neuropathological criteria. Finally, our pathological diagnoses were obtained by pathologists who had access to clinical information; therefore, clinical diagnosis and pathological diagnosis were not completely independent.

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Author contributions: Study concept and design (Drs Knopman, Salviati, and Rocca); acquisition of data (Drs Apaydin, Salviati, and Rocca); analysis and interpretation of data (Drs Knopman, Parisi, Boeve, Salvadri, Edland, and Rocca and Ms Cha); drafting of the manuscript (Drs Knopman, Parisi, and Rocca and Ms Cha); critical revision of the manuscript for important intellectual content (Drs Knopman, Parisi, Boeve, Apaydin, Salvadri, Edland, and Rocca); statistical expertise (Drs Knopman, Edland, and Rocca and Ms Cha); administrative, technical, and material support (Drs Salvadri and Rocca); and study supervision (Dr Rocca).

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This work is dedicated to the memory of Emre Kolin, MD, who was the principal founder of the Mayo Alzheimer’s Disease Patient Registry.

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