Survival Study of Vascular Dementia in Rochester, Minnesota

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Objective: To investigate the relationship between features and definitions of vascular dementia (VaD) and survival.

Design: We used the medical records linkage system of the Rochester Epidemiology Project to identify incident cases of dementia in Rochester from January 1, 1985, through December 31, 1989. Dementia and Alzheimer disease were defined using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Vascular dementia was defined by ad hoc criteria, including imaging. Each patient with dementia was matched by age and sex to a referent subject free of dementia. Patients with dementia and referent subjects were followed from the onset of dementia (or index year) through death, censoring, or the end of the study.

Results: We included 479 patients with incident dementia and 479 referent subjects. Overall, patients with VaD had worse mortality than referent subjects (relative risk [RR], 2.7; 95% confidence interval [CI], 1.9-3.9). Among patients with VaD, those with dementia temporally related to a stroke had a worse relative mortality (RR, 4.5; 95% CI, 2.7-7.4) than those with only imaging evidence of bilateral infarctions in gray matter structures (RR, 2.4; 95% CI, 1.5-3.8). Relative mortality estimates varied by using 3 sets of published diagnostic criteria for VaD. Patients with VaD had a higher RR of death (RR, 2.7; 95% CI, 1.9-3.9) than patients with dementia overall (RR, 1.8; 95% CI, 1.6-2.1) or patients with Alzheimer disease (RR, 1.4; 95% CI, 1.2-1.7).

Conclusions: The relative mortality of patients with VaD varied depending on the set of diagnostic criteria used. A temporal relationship to a stroke was the strongest predictive feature for poor survival in patients with dementia.

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Dementia is associated with increased mortality.1-6 However, information on the mortality of patients with specific types of dementia is limited, particularly for vascular dementia (VaD). Some studies7,8 have claimed that patients with VaD have a less favorable survival than those with Alzheimer disease (AD), while others3,4,6,9 have failed to show such a difference. Because cerebrovascular disease is consistently associated with reduced survival,10-13 it is puzzling that VaD has not been uniformly associated with reduced survival. A possible explanation for this inconsistency is that the diagnostic criteria misclassify patients who actually have AD pathologically as patients with VaD, thus causing a dilution of the impact of cerebrovascular disease on survival.

We investigated patterns of long-term survival in 479 patients with incident dementia who had symptom onset from 1985 through 1989.14,15 At the time of the study, most patients with dementia were deceased. In particular, we compared the relative survival of patients with VaD, and with specific definitions of VaD, with the survival of patients with AD and of patients with dementia overall.

Methods

Patients with Dementia

We used the medical records linkage system of the Rochester Epidemiology Project to identify all subjects residing in Rochester who developed dementia from January 1, 1985, through December 31, 1989. Details about the study population and the identification of incident cases were reported elsewhere.14,15 Age- and sex-specific incidence rates of dementia, AD, and VaD in the Rochester population were reported previously.14,15 To be included in the study, patients with dementia were required to reside in Rochester during the year of onset of dementia and for at least 1 preceding year. Patients who moved to Rochester for the management of a preexisting dementia-related illness were excluded.
Information for the diagnosis of dementia and for the classification of patients by type of dementia was abstracted from the medical history, neurological examination results, and neuroimaging studies, as collected historically in the patient dossiers of the records linkage system. Historically, most patients were not seen by neurologists or behavioral neurology subspecialists; therefore, many medical records did not include a formal cognitive assessment. The details available about the severity of the symptoms differed across patients. Because of these limitations, we were unable to measure the severity of dementia at diagnosis in terms of cognitive performance or activities of daily living. The diagnostic criteria for dementia were those of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The criteria for dementia in DSM-IV include memory impairment as a prominent early feature; at least 1 of the following: aphasia, apraxia, agnosia, or disturbance of executive function; and loss of function sufficient to interfere with social or occupational activities. The criteria were scored separately, and dementia was diagnosed only if all of the requirements for the diagnosis were fulfilled. Subjects with a medical record suggestive of dementia, but with incomplete documentation of the DSM-IV criteria for dementia, were considered to not have dementia and were excluded (n = 14). Alzheimer disease was also defined by the DSM-IV criteria.

Based on our prior work, we defined VaD by either 1 of the following criteria: (1) dementia onset or worsening within 3 months of a clinical stroke or (2) bilateral gray matter infarctions, shown by imaging, that fulfilled specified location criteria (described later). It was not possible to review the actual computed tomographic or magnetic resonance imaging scans of our patients; however, the primary study neurologist (E.K.) reviewed the radiologists' written reports of these studies. Most imaging studies were computed tomographic scans; only 7.9% of the patients who underwent imaging (28 of 354 patients) had at least 1 magnetic resonance imaging scan. We classified infarctlike lesions as likely to undermine cognition (which we will refer to as critical lesions) when they fulfilled 1 of the following 2 criteria: (1) bilateral frontal, temporal, or parietal lobe cortical infarctions or (2) bilateral thalamic or basal ganglia infarctions. We refer to these criteria as the Mayo Clinic criteria. We also independently applied 3 sets of published diagnostic criteria for VaD: DSM-IV criteria, National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS–AIREN) probable VaD criteria, and International Classification of Diseases, 10th Revision (ICD-10) 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.

REFERENT SUBJECTS

Each one of the 420 patients with dementia not caused by other medical or neurological diseases was individually matched by age (±1 year) and sex to a general population referent subject, drawn randomly from all the subjects residing in Rochester and free of dementia in the index year (year of onset of dementia in the matched patient). The list of all Rochester residents from whom potential referent subjects were drawn was provided by the records linkage system and was based on the enumeration of all individuals in contact with the system at least once in the 3 years after the index year. Potential referent subjects were selected randomly among all residents fulfilling the matching criteria. For the 59 patients with dementia secondary to a medical disease or a neurological disease other than AD, VaD, or another type of primary dementia, virtual referent subjects of the same age and sex were imputed using the published life tables for Minnesota in 1990. Referent subjects were assigned the onset age of their matched patients as the starting point for survival analyses.

DATA ANALYSIS

The passive follow-up of patients and referent subjects was conducted by manually abstracting medical records in the records linkage system. For the 59 virtual referent subjects, the outcome was imputed from the life tables. Subjects who did not die during the follow-up were censored alive either when they moved out of the system or at the most recent medical record abstraction (end of the study). The end of the study date varied among subjects; however, 87.3% of patients and 73.1% of referent subjects were deceased by the end of the study. Medical record abstraction was completed in early 1998.

We constructed Kaplan-Meier survival curves for patients and referent subjects, with death from any cause as the event of interest. The relative risk (RR) of death in patients with dementia compared with referent subjects and its 95% confidence interval (CI) were estimated using Cox proportional hazards models, with adjustment for age at the onset of dementia (in 4 quartiles) and sex. For comparisons across different features of VaD, or across different definitions of VaD, we graphed several survival curves in the same figure (patient-to-patient comparisons). Comparisons of survival curves across groups of patients were conducted using Cox proportional hazards models. All comparisons were adjusted by age of onset of dementia (in 4 quartiles) and sex to remove their possible confounding effect.

The proportionality assumption was tested visually and by introducing a time-dependent coefficient in the Cox proportional hazards model. All statistical testing was performed at the conventional 2-tailed α level of .05. Data were analyzed using SAS statistical software.

The patients and referent subjects included in this study were originally identified as cases and control subjects for a case-control study nested within a cohort. Therefore, patients were sampled conditionally on being alive at the onset of dementia (onset year) and when the diagnosis was established (diagnosis date). By contrast, referent subjects were selected conditionally on being alive only in the year of onset of dementia in the matched patient. A few referent subjects died or were censored alive between the onset year and the diagnosis date. To avoid this time mismatch, we conducted secondary analyses starting survival at the date of diagnosis rather than at the year of onset. Referent subjects were assigned the same date of diagnosis as their matched patients, and those who died or were censored between the onset year and the diagnosis date were excluded from the analyses. These secondary analyses yielded similar results; therefore, only our primary results are reported extensively.

RESULTS

We found 482 patients with the onset of dementia from 1985 through 1989 in Rochester. We excluded 3 patients because of their extreme age (>100 years) and the inability to find adequate referent subjects. The remaining 479 patients were matched to 479 referent subjects; 420 referent subjects (87.7%) were specified individuals from the same Rochester population, while 59 (12.3%) were virtual individuals imputed from the life tables. Among the 479 patients, 330 were women (68.9%) and 149 were men (31.1%). At the onset of dementia, 40 patients (8.4%) were aged 50 to 69 years, 133 (27.8%) were...
aged 70 to 79 years, 232 (48.4%) were aged 80 to 89 years, and 74 (15.4%) were 90 years or older (median age of onset, 82 years). At the time of this study, there were 418 deaths among patients (87.3%) and 350 deaths among referent subjects (73.1%).

Table 1 shows the RRs of death as a function of different types of dementia. The median survival from onset was 5.2 years for subjects with all types of dementia and 7.5 years for referent subjects. Men had a worse relative mortality than women. The RR of dying decreased with advancing age at onset of dementia (significant linear decreasing trend of the log RRs, \( P < .001 \)).

The median survival from onset was 6.1 years for patients with probable AD and 7.2 years for their referent subjects. The median survival from onset was 3.3 years for patients with VaD (by the Mayo Clinic criteria) and 7.1 years for their referent subjects. Figure 1 compares the relative mortality in patients with dementia overall, those with AD, and those with VaD (by the Mayo Clinic criteria).

Table 2 shows the RR of death by different cerebrovascular features and by different criteria for VaD. Patients in whom dementia occurred or worsened within 3 months of a stroke had a high relative mortality, whereas patients with a history of more than 1 stroke not necessarily related to dementia onset or worsening had a lower relative mortality. Imaging evidence of gray matter infarctlike lesions had a lower impact on survival. When imaging evidence of cerebrovascular disease included white matter lesions, as specified by the NINDS-AIREN imaging criteria, survival further improved.

By using dementia overall as a reference for patient-to-patient comparisons, and adjusting for age and sex, the RR of death was 1.4 (95% CI, 1.1-1.8) for patients with any history of stroke, 1.6 (95% CI, 1.1-2.1) for patients with critical imaging lesions, excluding white matter lesions, and 2.3 (95% CI, 1.7-3.1) for patients with stroke temporally related to dementia. All RRs were statistically significant (Figure 2).

Different diagnostic criteria for VaD influenced greatly our survival findings (Table 2). When dementia temporally related to stroke was included as an obligate feature of the criteria, as in the NINDS-AIREN criteria, the RR was high. When the temporal relationship was
not part of the VaD definition, as in the DSM-IV criteria, survival was better. In addition, inclusion of white matter lesions in the diagnostic criteria improved mortality. For example, when white matter lesions were included in the DSM-IV criteria, the RR of dying for VaD (1.9) was barely worse than for AD (1.4).

Considering AD as a reference for patient-to-patient comparisons, and adjusting for age and sex, the RR of death for VaD was 1.5 (95% CI, 1.2-1.9) using the DSM-IV criteria, including white matter lesions; 1.6 (95% CI, 1.3-2.0) using the ICD-10 criteria; 2.2 (95% CI, 1.7-2.8) using the Mayo Clinic criteria; and 4.6 (95% CI, 2.8-7.5) using the NINDS-AIREN criteria. All RRs were statistically significant (Figure 3).

We studied survival in patients with VaD and found that dementia onset or worsening temporally related to a stroke was a major predictor of survival. Patients with this feature had much higher RRs of death compared with patients with AD. Neither a history of stroke (with or without a temporal relationship) nor the presence of infarct-like...
lesions on imaging increased mortality to the same degree. Allowing white matter lesions to be included as sufficient evidence for cerebrovascular disease substantially reduced the relative mortality. When defining VaD by various diagnostic criteria, survival was worst when the temporal relationship of stroke to dementia was required, such as in the NINDS-AIREN criteria for probable VaD. The difference between our observations and the variable findings previously reported in the literature about the survival of patients with VaD\textsuperscript{4,6,8} can be traced back to the choice of VaD diagnostic criteria.

Our findings of mortality differences as a function of sex and age in patients with dementia overall were similar to the findings of others.\textsuperscript{1,3,4} It has been argued that patient identification through our records linkage system could cause an undercounting of patients with mild dementia. If our method undercounted patients with mild dementia, such a bias should have caused a decreased survival rate. Our overall median survival from diagnosis for patients with dementia (4.1 years) was shorter than that from the Canadian Study of Health and Aging (6.6 years),\textsuperscript{6} but similar to that from a cohort in southern France (4.5 years).\textsuperscript{3} Both of these studies had median ages at onset of dementia comparable to our cohort. Our survival rate from diagnosis for AD (4.6 years) was shorter than that from the Consortium to Establish a Registry for Alzheimer’s Disease (5.9 years);\textsuperscript{2} however, our subjects were much older (median age of onset, 82 vs 73 years). Because of the age difference, it is not clear that our subjects were more impaired than the patients from the Consortium to Establish a Registry for Alzheimer’s Disease.

Our findings were subject to biases inherent in any survival study in which symptom onset and disease diagnosis are separated in time. Secondary analyses using the date of diagnosis as a starting point and excluding those referent subjects who died between the onset and the diagnosis of dementia in the matched patient did not modify our findings. The relative comparisons of clinical criteria and diagnostic features were virtually identical whether symptom onset or diagnosis of dementia was used as the starting point (results not shown).

Another limitation introduced by the lag between symptom onset and diagnosis is the length bias. Length bias refers to the failure to include patients who developed dementia but died before being detected. An analytic strategy that accounted for length bias was used by the Canadian Study of Health and Aging.\textsuperscript{6} That report showed that the survival rate for patients with all forms of dementia was 65.2%, and the specificity was 86.4%.\textsuperscript{27} Among the patients in our study, 46% had mild dementia at the time of death. We were unable to determine the reason for the difference, but it may reflect a difference in severity of dementia.

The major weakness of this study was the retrospective assignment of dementia diagnoses, a topic dealt with in earlier publications.\textsuperscript{14-18} Another weakness of our study was the use of routine reports of imaging studies, rather than the actual scans. Most of the imaging tests were computed tomographic scans. Because computed tomography is less sensitive to small lesions than magnetic resonance imaging, we detected only relatively large infarctlike lesions and white matter lesions. Finally, 114 (27.1%) of our 420 patients with dementia not caused by other medical or neurological diseases underwent no imaging study. The trends in our data suggest that had everyone undergone magnetic resonance imaging, we would have discovered more silent infarcts and the RRs for mortality as a function of infarctlike lesions would have decreased. In addition, because we were unable to measure dementia severity at diagnosis, we could not investigate the impact of severity on mortality. Dementia severity, as measured by either a clinical scale or an activity of daily living scale, influenced survival in another study.\textsuperscript{2} Therefore, dementia severity at diagnosis may have confounded some of our patient-to-patient comparisons. However, the negative prognostic effect of the temporal relationship between dementia and stroke seems quite striking, even assuming some possible confounding by severity.

Cerebrovascular disease is associated with increased mortality.\textsuperscript{10-13} Therefore, the presence of cerebrovascular disease should influence the prognosis in patients with dementia. However, the relationship may be complex because none of the patients in this series who had dementia temporally related to stroke and underwent autopsy actually died of a stroke. More than half of the patients with dementia temporally related to stroke had a cardiac cause of death. This compares to approximately a third of cardiac causes of death for the remainder of the autopsied patients.

Actual clinical strokes are probably the best indicators of cerebrovascular disease. Focal neurological signs or white matter lesions, even if extensive, may not be sufficiently specific for cerebrovascular disease, and they do not modify survival in any major way. Even a clinical history of stroke itself, or bilateral gray matter infarctions by imaging, had less impact on survival than the temporal relationship between stroke and dementia (onset or worsening of dementia within 3 months of a stroke).

In an autopsy study of 89 of the patients described herein, 12 had pure VaD and 11 had a combination of VaD and AD. The sensitivity of the Mayo Clinic VaD criteria for all VaD (pure plus combined with AD) was 65.2%, and the specificity was 86.4%.\textsuperscript{27} Among the autopsied patients, there was no difference in duration of dementia between those with pure VaD and those with combined VaD and AD. While the ultimate standard for comparison in the validation of a set of diagnostic criteria is usually an autopsy, the predictive value of the criteria for mortality is also important in clinical practice. The feature of dementia temporally related to stroke had a good predictive value for increased mortality in our study. We acknowledge that a history of stroke or imaging evidence of infarction could simply indicate worse generalized vascular disease that has no brain disease specificity. Even if the excess mortality in patients with
certain stroke features is driven largely by cardiovascular disease outside of the brain, our findings provide prognostic insights useful to clinicians.

Dementia following stroke is common and has strong face validity as a diagnostic marker for VaD.28-31 The present study extends the relevance of this clinical feature by the demonstration of the reduced survival associated with dementia that follows stroke.

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