Vascular Dementia
Incidence and Risk Factors in the Canadian Study of Health and Aging

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Background and Purpose—Very few population-based studies have systematically examined incident vascular dementia (VaD). From the Canadian Study of Health and Aging cohort, incidence rates of VaD were determined and risk factors analyzed.

Methods—This was a cohort incidence study that followed 8623 subjects presumed to be free of dementia over a 5-year period. The risk factors were examined with a nested prospective case-control study. Exposure was determined by means of a risk factor questionnaire administered to the subject or a proxy at the beginning of the study.

Results—On the basis of 38 476 person-years at risk, the annual incidence rate was estimated to be 2.52 per thousand undemented Canadians (95% CI 2.02 to 3.02). Including an estimation of the probability of VaD among the decedents, this figure rose to 3.79. For the risk factors study, 105 incident cases of VaD according to the NINCDS-AIREN criteria were compared with 802 control subjects. Significant risk factors were: age (OR = 1.05), residing in a rural area (2.03), living in an institution (2.33), diabetes (2.15), depression (2.41), apolipoprotein E ε4 (2.34), hypertension for women (2.05), heart problems for men (2.52), taking aspirin (2.33), and occupational exposure to pesticides or fertilizers (2.05). Protective factors were eating shellfish (0.46) and regular exercise for women (0.46). There was no relation with sex, education, or alcohol.

Conclusions—The study confirmed some previously reported risk factors but also suggested new ones. It raised concerns about the prescription of aspirin and perhaps other factors related to rural life. (Stroke. 2000;31:1487-1493.)

Key Words: cerebrovascular disorders ■ epidemiology ■ cohort ■ case-control

After Alzheimer’s disease (AD), vascular dementia (VaD) is the second leading cause of dementia. Despite the fact that this type of dementia is theoretically preventable by controlling vascular factors, little is known about its underlying cause. Few studies and none in North America have reported specific incidence figures for VaD. The majority of the studies on risk factors were carried out with prevalent cases. These studies should be interpreted cautiously because some risk factors could be wrongly identified, being associated with survival instead of the development of the disease (Neyman bias). Also, in these studies, information on exposure was gathered from a proxy when the diagnosis was already known. Thus, the information is less precise and subject to biases. Only a few longitudinal studies that used incident cases of VaD have been published to date. The number of VaD cases in these studies was usually <50, thus limiting the power to identify clinically important risk factors.

Risk factors for prevalent VaD have been reviewed by many authors over the last 4 years.1–4 They can be divided into 4 categories: (1) demographic: older age, race/ethnic group (Asian), sex (male), low education, rural area; (2) atherogenic factors: hypertension, cigarette smoking, heart disease, diabetes, hyperlipidemia, carotid bruits, menopause without estrogen replacement therapy; (3) nonatherogenic factors: genetic, alteration in hemostasis, high alcohol consumption, use of aspirin, psychological stress, occupational exposure (pesticides, herbicides, liquid plastic, or rubber), socioeconomic factors (blue collar); and (4) stroke-related factors: volume of cerebral tissue loss, infarct location and number.

The second phase of the Canadian Study of Health and Aging (CSHA) provides a unique opportunity to study risk factors associated with incident VaD in a population-based study designed to estimate the incidence of different types of dementia in Canada.

Subjects and Methods

Sample
The design of the CSHA has been described in detail elsewhere.5,6 Briefly, in the first phase of this study (CSHA-1: 1991 to 1992), subjects were recruited from both the community and institutions on

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Incidence Rate Calculations

Incidence rates were calculated for Canada except Newfoundland and omitting nonparticipants in CSHA-2 and those who were screened positive at CSHA-2 but were not clinically examined. Because dementia is mainly irreversible and highly prevalent in the older population, we used the estimated population without dementia in Canada in 1991 as the denominator rather than the total Canadian population. Estimated population without dementia was calculated with the use of the prevalence estimates from CSHA-1. Standard actuarial methods were used to estimate person-years at risk, and these figures were weighted according to the sampling frame. The date of onset of dementia was assumed to be midway between the date of the baseline assessment and the date of the follow-up assessment. CIs for the estimates were calculated considering rates as Poisson variables. These incidence figures were first calculated on survivors only and are thus underestimated because the 5-year delay between the 2 assessments allowed incident cases to die before the second assessment. For deceased subjects, it was possible to estimate the incidence of dementia in general from 3 sources: death certificates, decedent interview with a relative, and a regression model developed from the 71 people who died within 3 months of undergoing the CSHA-1 diagnostic examination. However, it was not possible to refine the diagnosis of dementia to identify VaD. We estimated the rates of VaD among decedents, applying the same relative increase in age-sex rates obtained for dementia in general. This is probably an underestimate, because survival from VaD is less than from AD.

Risk Factor Analysis

The risk factor study used a prospective case-control design nested within the CSHA cohort study. Eligible subjects were CSHA participants presumed to be cognitively intact in 1991 on the basis of the 3MS score (>77) that they obtained at screening and those not diagnosed as demented in 1991 after the clinical examination. Cases were subjects with a Consensus New Criteria diagnosis of VaD at CSHA-2. AD subjects with vascular components (mixed dementia) were not included as cases. Control subjects were the subjects who underwent the clinical examination at CSHA-2 and were judged cognitively normal according to the same New Consensus Criteria. Data on the risk factors were obtained primarily from the Risk Factor Questionnaire completed in 1991 by the subject himself/herself when he/she was presumed to be free of dementia. The questionnaire covered occupational and environmental exposure, lifestyle (including smoking, alcohol, and a limited dietary history), and family and medical history (including antecedent and medication use). For some subjects who did not complete it, the Proxy Risk Factor Questionnaire was used. For some variables (medication use and history of stroke, diabetes, high blood pressure, heart problems, and Parkinson’s disease), data from the 1991 screening interview or clinical examination were also used. The APOE phenotype was analyzed on subjects for whom a blood test was available.

Because the control subjects were unequally distributed between regions of Canada and the incidence rates did not differ from one region to another, the analyses were adjusted for region. The relation of VaD with age, sex, and education was first investigated to see if they could be confounders in the relation between VaD and the different risk factors. Bivariate analyses were conducted considering each risk factor separately as the explanatory variable. ORs and 95% CIs were based on the likelihood-ratio test with unconditional logistic regression models (LOGISTIC procedure, SAS/STAT software, SAS Institute Inc). Because the type I error was set at 5%, the OR is statistically significant when its 95% CI does not include 1 (null value). Interactions with age and sex were systematically verified, and only those statistically significant are reported. Some other interactions (eg, stroke, vascular factors) hypothetically driven were also verified.

Results

The Figure summarizes the flow of the subjects through the 2 phases of the CSHA study. Of the 10 263 subjects in the

Diagnostic Assessment

For all subjects who underwent a CSHA-2 clinical assessment, a first diagnosis was reached in the same way as in CSHA-1. Briefly, a nurse first administered the 3MS examination, assessed hearing, vision, vital signs, height, and weight, collected information on medication use, and gathered the subject’s cognitive and family history by using Section H of the CAMDEX history interview. A blood sample was collected to be genetically tested for apolipoprotein E (APOE) genotypes. Next, a trained physician with special expertise in dementia (neurologist, psychiatrist, geriatrician, general internist, or general practitioner) recorded a standard history and physical examination and completed the Hachinski Ischemia Scale, for which a score of 7 was considered indicative of vascular dementia. On the basis of these data including a summary of the nurse’s basic evaluation, the physician arrived at a preliminary diagnostic opinion. Dementia and its severity were diagnosed according to the criteria of the DSM-III-R. AD was diagnosed with the use of the NINCDS-ADRDA criteria. Vascular dementia was diagnosed according to the ICD-10 criteria without routine neuroimaging. All subjects with a 3MS score ≥50 proceeded to neurological testing in which a psychometrician, blinded to the 3MS score from the interview, administered a battery of neuropsychological tests. This battery (described elsewhere) included specific tests to assess memory, language, attention, visual perception, construction, and problem solving. A neuropsychologist, blinded to the physician’s examination, evaluated the test results in conjunction with the results of the CAMDEX and the 3MS examination administered by the nurse and formed his/her preliminary diagnosis also using DSM-III-R (for dementia), NINCDS-ADRDA (for AD), and ICD-10 criteria (for VaD). All data were reviewed at a case conference to reach the consensus diagnosis with the use of the same criteria described above. The consensus diagnosis of VaD based on ICD-10 criteria was used to calculate the incidence figures of VaD.

In CSHA-2, all subjects with a preliminary diagnosis of vascular dementia (or AD with vascular components) were asked to have a CT scan. Moreover, since CSHA-1, new diagnostic criteria had been proposed. Thus, after the first consensus diagnosis was reached, additional information (CT scan, new neuropsychological tests) was made available to the physician and neuropsychologist at the case conference, and a second diagnosis, called the Consensus New Criteria diagnosis, was made with the use of the DSM-IV criteria and NINDS-AREN criteria. These criteria were used to identify subjects for the risk factor study.
CSHA-1 sample, dementia status was unknown for 508 subjects (screened positive but did not attend clinical examination), 1132 were demented at baseline and hence ineligible for the incidence study, 1939 died between the 2 phases of the study, and 235 were lost to follow-up. From the 6449 subjects alive at CSHA-2, 26 died between the screening and the clinical assessment and 676 refused to participate or were not contacted either in the screening or in the clinical interview, for a participation rate of 89.5% (5747 of 6423). Details on the characteristics of the nonparticipants are reported elsewhere.6

A total of 38 476 person-years were followed over the 5-year period. From the 492 cases of dementia identified, 97 (20%) were diagnosed as VaD by CSHA-1 criteria, for an annual incidence rate of VaD of 2.52 per 1000 undemented persons (95% CI 2.02 to 3.02). Tables 1 and 2 detail incidence rates by sex for each age strata. For the Canadian (except Newfoundland) population, it can be estimated that 7355 new cases of VaD survived over the 5-year period. With the use of the adjustment method to take mortality rates into account, the incidence rate would be 3.79, increasing the number of new cases in Canada to 11 062 over the 5-year period.

For the risk factor study, 105 incident cases of VaD were identified with the NINCDS-AIREN criteria and compared with the 802 control subjects who were diagnosed without cognitive impairment. There were 4 cases fulfilling the ICD-10 criteria who did not meet the new criteria and 12 new cases not previously identified with the ICD-10 criteria. The mean age of the cases was 78.1 years (SD 6.04), which was slightly but significantly (P=0.003) older than the control subjects (76.0; SD 6.6). Adjusting for region, the OR associated with age was 1.05 (95% CI 1.02 to 1.08) per year. The proportion of men was 39.0% in the cases and 42.3% in the control subjects (P=0.53). The mean number of years of schooling was 10, and there was no significant difference (P=0.12) between cases (9.7; SD 4.4) and control subjects (10.4; SD 4.0). Hence, all subsequent analyses were adjusted for age and region.

Thirteen (12.4%) incident cases were living in institutions at CSHA-1 compared with 48 (6.0%) of the control group (P=0.014). A larger proportion of cases was living in rural areas (18.3% versus 10.8%; P=0.024). A proportion of 26.7% (28 subjects) of the cases reported in 1991 having had a stroke, as opposed to only 5.4% (43 subjects) of the control group. Table 3 shows the results for each of the risk factors. Significant risk factors were living in a rural area (2.03) or an institution (2.33), having diabetes (2.15), taking aspirin (2.33), APOE e4 allele (2.34), exposure to pesticides or fertilizers (2.05), and having depression (2.41). Hypertension was a risk factor only for women (2.05), whereas heart disease was significantly associated with VaD only for men (2.52). Significant protective factors were eating shellfish at least once per month (OR=0.46), smoking cigars nearly every day (0.20), and being engaged in regular exercise for women only (0.46). Some factors previously identified in other studies were not confirmed (male sex, cigarette smoking, alcohol, education, exposure to liquid plastic and rubber, menopause without estrogen replacement therapy).

We explored more deeply the relation between aspirin and VaD because aspirin is frequently prescribed in stroke and...
other vascular diseases. Surprisingly, the OR was significant only in subjects without stroke (OR = 2.49; 95% CI 1.46 to 4.21), heart problems (OR = 2.59; 95% CI 1.47 to 4.49), diabetes (OR = 2.65; 95% CI 1.62 to 4.32), or high blood pressure (OR = 2.52; 95% CI 1.35 to 4.67).

**Discussion**

This study is the largest population-based incidence study and one of the few North American studies published to date on vascular dementia. Age-specific incidence rates were similar to most of the studies reported. However, rates were much lower than those reported in 3 previous studies from Lundby (Sweden), Hisayama (Japan), and Cambridge (England). Only a systematic comparison of incidence studies taking into account methodological characteristics of the studies (sampling, diagnostic criteria, inclusion of death), epidemiology of cerebrovascular disease, and CI of the estimates could determine if these differences are real and possibly related to country-specific exposures. Nevertheless, the incidence figures reported in this study are probably underestimated as the result of false-negatives on the screening test and the absence of neuroimaging, which may have contributed to underdiagnosis of VAD.

This study is also the largest risk factor study ever published on VaD with incident cases from a population-based study. Control subjects were selected from the same cohort as cases, with the same procedure used for clinical assessment. Cases were identified by means of the NINDS-AIREN criteria, including neuroimaging data. However, some limitations must be acknowledged. First, because 5 years elapsed between the 2 phases of the study, losses to follow-up and mostly mortality could have introduced some bias. Given that the median survival of VaD is estimated to be 5 years after the diagnosis and much lower than the expected survival of the control subjects, a selection bias could have occurred. Incident cases who died early are not included in this study, and factors associated with rapid course VaD cannot be identified. Also, some factors associated with longer survival of cases may be falsely identified as risk factors, although this problem is less important than in prevalence studies. Second, some risk factors previously reported in other studies were not assessed in this study by means of a risk factor questionnaire (eg, high hematocrit, low blood pressure, alteration in hemostasis, presence of carotid bruits, ECG abnormalities). Third, the questionnaire was crude for some variables (nutrition and environmental exposure), and measurement error may have attenuated the associations. Finally, missing data on exposure could be a source of significant potential biases. This problem also precludes the use of multivariate modeling.

The association of VaD with age is consistent with most of the incidence studies although less striking than for AD. There was no risk associated with sex in this study. Although none of the previously published incidence studies found a significant risk for sex, all reported ORs for male sex are ≥ 1.5, but given the small sample size of these studies, the CI for this estimate was very large. This study confirms previous studies relating VaD to diabetes, heart disease, and hypertension. However, the sex interactions for heart condition and high blood pressure are surprising. Only Aronson et al reported that previous myocardial infarction was associated with VaD for women only, whereas in our study the association with heart condition was significant only for men. It was the association with hypertension that was significant only for women. These interactions weaken any conclusions about heart disease and high blood pressure.

The risk associated with institutions was related to the high prevalence of strokes in these settings because risk is no longer significant when adjusting for strokes.

The absence of a relation of VaD with cigarette smoking, although raised in some prevalence studies, confirmed the data from the CSHA prevalence study and those of Yoshitake et al from another incidence study. The protective effect of cigar smoking observed in the present study has never been reported but should be interpreted with caution because it was based on only 1 case. Alcohol was also not associated with significant risk, contrary to the prevalence data from CSHA and the incidence study from Yoshitake et al.

The association of VaD with aspirin consumption confirms the finding of the analysis carried out with prevalent cases. The authors suggested that this association could have been related to Neyman’s bias, with aspirin prolonging the survival of patients with VaD. Although this phenomenon also could be present in this study, given the large interval between the 2 phases of the study, the magnitude of the risk is striking (2.3) and not very different from the estimate of the prevalence study (3.1). The risk associated with aspirin was not as first suspected, a marker for stroke and cardiovascular diseases. Because aspirin is widely prescribed, it would be

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No. of Cases</th>
<th>Person-Years at Risk†</th>
<th>Rates Among Survivors†</th>
<th>95% CI</th>
<th>Estimated Rates, Including Deaths†</th>
</tr>
</thead>
<tbody>
<tr>
<td>65–69</td>
<td>2</td>
<td>1697</td>
<td>1.18</td>
<td>0.00 to 2.81</td>
<td>2.23</td>
</tr>
<tr>
<td>70–74</td>
<td>10</td>
<td>3257</td>
<td>3.07</td>
<td>1.17 to 4.97</td>
<td>4.61</td>
</tr>
<tr>
<td>75–79</td>
<td>9</td>
<td>2559</td>
<td>3.52</td>
<td>1.22 to 5.81</td>
<td>6.63</td>
</tr>
<tr>
<td>80–84</td>
<td>11</td>
<td>2093</td>
<td>5.26</td>
<td>2.15 to 8.36</td>
<td>7.01</td>
</tr>
<tr>
<td>≥85</td>
<td>8</td>
<td>1204</td>
<td>6.64</td>
<td>2.04 to 11.25</td>
<td>8.28</td>
</tr>
<tr>
<td>All</td>
<td>40</td>
<td>14,281</td>
<td>2.80</td>
<td>1.93 to 3.67</td>
<td>4.19</td>
</tr>
</tbody>
</table>

*Weighted to be representative of the 1991 undemented Canadian population (except Newfoundland).
†Annual rate per 1000 undemented Canadians (except Newfoundland).
important to further clarify the role of aspirin in the pathogenesis of VaD.

The absence of an association with education is consistent with most of the recent incidence studies of VaD and dementia in general. The risk associated with low education suggested in many prevalence studies including CSHA was probably related to the effect of education on the cognitive screening test and on the neuropsychological battery used in these studies. Subjects with little education were more prone to be identified early as demented, thus artificially lengthening the course of the disease (lead-time bias).

The risk of VaD associated with previous episodes of depression was also reported by Katzman et al. It confirms the association observed in CSHA-1 by means of prevalence data. Further analysis shows that the risk is striking for subjects reporting a previous stroke (OR = 10.77; CI 2.23 to 40.60). Depression may be a premonitory syndrome for VaD in stroke patients or a marker of the importance of cerebral damage.

The association of VaD with the $e4$ allele of APOE was also reported in other studies. This raises the possibility that this allele is not a specific marker for AD but is associated with the repair processes in the nervous system. Given that APOE plays a role in normal brain metabolism, it can be hypothesized—as suggested by Frisoni et al—that different insults, either degenerative or vascular, might result in greater damage when $e4$ allele is present. However, since the diagnosis of pure VaD is only probable according to the NINDS-AIREN criteria, co-occurrence of AD is possible and may explain part of the association with APOE.

The risk associated with exposure to pesticides and fertilizers confirms the finding of the prevalence study and could explain part of the association with rural areas. Higher incidence of VaD in rural areas was also reported by Liu et al. Associations with these types of exposure were also reported for AD and Parkinson’s disease. A prospective study collecting detailed exposure data would be needed to shed more light on these associations.

The protective effect of estrogen replacement therapy in menopausal women was not confirmed in this study. However, the CI of this estimate was very large because very few women reported using estrogen among their medications. There was no specific question about estrogen replacement therapy in the questionnaire, and this medication could have

<table>
<thead>
<tr>
<th>TABLE 3. Risk Factors for Vascular Dementia</th>
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<tbody>
<tr>
<td>Risk Factor</td>
</tr>
<tr>
<td>Sex (male)</td>
</tr>
<tr>
<td>Residing in rural area</td>
</tr>
<tr>
<td>Living in an institution</td>
</tr>
<tr>
<td>Apolipoprotein E (any $e4$ allele)</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>High blood pressure</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Heart condition</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Takes or has taken aspirin</td>
</tr>
<tr>
<td>Estrogen replacement therapy</td>
</tr>
<tr>
<td>Has eaten shellfish at least once per month</td>
</tr>
<tr>
<td>Engages in regular exercise</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Has smoked cigarettes nearly every day</td>
</tr>
<tr>
<td>Has smoked cigars nearly every day</td>
</tr>
<tr>
<td>Has drunk beer at least once a week</td>
</tr>
<tr>
<td>Has drunk wine at least once a week</td>
</tr>
<tr>
<td>Has drunk spirits at least once a week</td>
</tr>
<tr>
<td>Occupational exposure to pesticides or fertilizers</td>
</tr>
<tr>
<td>Occupational exposure to plastic or rubbers</td>
</tr>
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</table>

*Adjusted for age and region.
been underreported. Finally, this study was the first to show the protective effect of eating shellfish and exercise (in women only). These associations need to be confirmed by other epidemiological studies, and the biological plausibility of these factors must be explored further.

In conclusion, this study provides relatively precise incidence rates for VaD, particularly in very old people. It confirms the important role of diabetes in the pathogenesis of VaD. It supports the hypothesis that depression could be an early symptom of VaD in stroke patients. It should raise concerns about the possible role of aspirin and pesticides and fertilizers in VaD. Some protective factors identified by this study should be further explored.

Acknowledgments

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References


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