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# Clinical Determinants of Dementia and Mild Cognitive Impairment following Ischaemic Stroke: The Sydney Stroke Study

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**Key Words**
Post-stroke dementia, clinical determinants · Vascular mild cognitive impairment · Vascular dementia · Magnetic resonance imaging brain scan

**Abstract**
***Background:*** Dementia following stroke is common but its determinants are still incompletely understood. ***Methods:*** In the Sydney Stroke Study, we performed detailed neuropsychological and medical-psychiatric assessments on 169 patients aged 50–85 years, 3–6 months after a stroke, and 103 controls with a majority of both groups undergoing MRI brain scans. Stroke subjects were diagnosed as having vascular mild cognitive impairment (VaMCI) or vascular dementia (VaD) or no cognitive impairment by consensus. Demographic, functional, cerebrovascular risk factors and neuroimaging parameters were examined as determinants of dementia using planned logistic regression. ***Results:*** 21.3% of subjects were diagnosed with VaD, with one case in those aged 50–59 years, 24% in those aged 60–69 years and 23% in those 70–79 years. There was no difference by sex. The prevalence of VaMCI was 36.7%. VaD subjects had lower premorbid intellectual functioning and had 0.9 years less education than controls. The VaD and VaMCI groups did not differ from the no cognitive impairment group on any specific cerebrovascular risk factor, however overall those with impairment had a greater number of risk factors. They did not differ consistently on depression severity, homocysteine levels and neuroimaging parameters (atrophy, infarct volume and number of infarcts) except for an excess of white matter lesions on MRI and greater number of infarcts in the VaD and VaMCI groups. On a series of logistic regression analyses, stroke volume and premorbid function were significant determinants of cognitive impairment in stroke patients. ***Conclusion:*** Post-stroke dementia and MCI are common, especially in older individuals. Cerebrovascular risk factors are not independent risk factors for VaD, but stroke volume is a significant determinant of dementia. Premorbid functioning is a determinant of post-stroke impairment.



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## Introduction

It is well recognised that stroke increases the risk of dementia, with rates of post-stroke dementia from 6 to 32% being reported in clinical samples in various studies [1, 2]. In a more recent epidemiological study, the 10-year risk of dementia after stroke was estimated at 19.3%, compared to 11.0% in non-stroke controls [3]. This two-fold increase in dementia following stroke is in contrast with a ninefold increase reported in some previous studies [1]. The large variation in rates is accounted for by variations in the populations studied as well as the criteria used for the diagnosis of dementia. As the definition of vascular dementia (VaD) is currently being refined [4], it is timely that these studies be revisited. One aspect of this reassessment is the consideration of vascular mild cognitive impairment (VaMCI) in stroke patients, which has thus far received little attention.

The clinical determinants of post-stroke dementia remain incompletely understood despite previous studies [2]. Increasing age and low education have consistently emerged as risk factors. Other factors that have variably been reported as significant determinants include risk factors for cerebrovascular disease, prior pathology, stroke features and infarct characteristics. The variability of the findings has prevented a consensus being reached on the most relevant factors in predicting the development of VaD.

The aim of this study was to describe a comprehensively examined cohort of stroke patients, who did not have evidence of progressive cognitive impairment greater than a pre-determined threshold prior to the index stroke, to identify the clinical features associated with the development of VaMCI and VaD. We hypothesised that age, education, pre-stroke cognitive decline, stroke volume, number of strokes, baseline cerebral atrophy, and non-infarct white matter pathology would all be significant determinants of mild cognitive impairment and dementia.

## Methods

*Sample*

Subjects were consecutive ischaemic stroke patients admitted over a 38-month period between May 1997 and June 2000 to two teaching hospitals. An ischaemic stroke was defined as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer, with no apparent cause other than of vascular origin' in which a brain CT or MRI scan does not show intracranial haemorrhage [5]. Two neurologists made the diagnosis of stroke independently. Subjects were aged 49–87 years, did not have a diagnosis of dementia or other neurological disorder prior to the stroke, did not have severe aphasia as a significant limiting factor for assessment (a score of <3 on the Aphasia Severity Rating Scale of the Boston Diagnostic Aphasia Examination) [6], and were well enough to consent to participate. Subjects had a score of <3.5 on the 16-item Informant Questionnaire of Cognitive Decline (IQCODE) [7] for the 5 years preceding the stroke. Healthy control subjects were unpaid volunteers, recruited from the same neighborhood as the stroke/TIA subjects, and matched for age, who had no history of stroke, TIA or other neurological or psychiatric disorder. An attempt was made to match subjects on sex and years of education, but this was not completely successful, the discrepancy being then taken into account in the analysis.

*Assessment Procedure*

The detailed procedures for this study have previously been published [8]. Stroke subjects had a baseline assessment within 1 week of admission to hospital, which included a detailed medical history and examination, history of risk factors for cerebrovascular disease and dementia, a functional assessment and the Mini-Mental State Examination (MMSE) [9]. The stroke type was classified according to the TOAST classification as large-artery atherosclerosis, small vessel occlusion (lacune) or cardioembolic stroke [10]. Localisation of stroke was classified as left or right, and as hemispheric, cerebellar or brain stem. Between 3 and 6 months after the index stroke, a detailed neuropsychological assessment and structured medical and psychiatric examinations were performed. The majority of subjects (66.7%) had a brain MRI scan. Control subjects were assessed at time of admission to the study.

*Neuropsychological Assessment*

The battery comprised the following tests pertaining to various cognitive domains (references for specific tests available from authors): verbal memory (Logical Memory I and II subtests from Wechsler Memory Scale – Revised, WMS-R); visual memory (Visual Reproduction I and II from WMS-R); working memory (Digit Span backwards, Arithmetic from Wechsler Adult Intelligence Scale Revised, WAIS-R); attention (Digit Span forwards, WAIS-R); Mental Control (WMS-R); language (15-item Boston Naming Test); information processing speed (Trail Making Test Part A, Symbol Digit Modalities Test); visuoconstruction (Block Design, WAIS-R, and copying simple figures); praxis-gnosis (Western Aphasia Battery ideomotor apraxia subtest items, finger gnosis and stereognosis); abstract reasoning (Similarities, Picture Completion, WAIS-R); mental flexibility (Colour Form Sorting Text, Trail Making Test Part B); verbal fluency (phonemic, FAS, and semantic, animals). Mental flexibility and verbal fluency were together characterised as 'executive function'. Premorbid ability was estimated using the National Adult Reading Test – Revised (NART-R), and handedness was determined with a modified version of Annett's Test. Trained clinical psychologists performed these assessments. Subjects judged to be clinically depressed were not tested until their depression had been satisfactorily treated as judged by a total score on the Geriatric Depression Scale (GDS) [11] of <5, a reduction in self-reported symptoms of depression, informant report and/or further psychiatric assessment.

*Medical and Psychiatric Assessment*

This comprised a medical history; a functional assessment (Social and Occupational Functioning Scale, SOFAS, Activities of Daily Living, ADL, and Instrumental ADL, IADL); a standard neurological examination (European Stroke Scale, ESS); detailed psychiatric assessment (past psychiatric history, Structured Clinical Interview for DSM-IV, 28-item General Health Questionnaire, 15-item GDS, Hamilton Depression Rating Scale, and Neuropsychiatric Inventory; references available from authors). A fasting blood sample was obtained for total plasma homocysteine (Hcy) levels. Total Hcy was measured using Abbot IMX-automated, fluorescence-based enzyme immunoassay with a range of measurement 0.5–50 μmol/l, and demonstrated high repeatability [12].

*MRI Scans*

MRI was performed on a 1.5-tesla Signa GE scanner (GE Systems, Milwaukee, Wisc., USA) using the following protocol: a scout mid-sagittal cut (2-D, TR 300 ms, TE 14 m; 5 mm thick, number of excitations 1.5); 1.5-mm-thick $T_1$-weighted contiguous coronal sections through whole brain using a FSPGR sequence and 3-D acquisition (TR 14.3 ms, TE 5.4 ms); 4-mm-thick (0 skip) $T_2$-weighted FLAIR coronal slices through whole brain (TR 8,900, TE 145, TI 2,200, FOV 25, 256 × 192).

*Analysis of Data*

Neuropsychological Tests

For the purposes of diagnosis and the classification of performance of each subject on each test, age-scaled scores were derived from published norms [13–17]. Where no published norms were available, impairment criteria were based on clinical judgement and discussed in consensus meetings. The tests were grouped into the cognitive domains described above. Years of education and performance on the NART-R were used as estimates of premorbid intellectual abilities. To determine an individual's performance on a test, the percentile was computed; performance below the 5th percentile was considered definite impairment, and between the 5th and the 10th percentile marginal impairment.

MRI Scans

MRI scans were transferred to an independent Windows NT workstation and analyzed using the software packages ANALYZE (Mayo Foundation, Rochester MI, USA) and SPM99 (Cognitive Neuroscience Group, National Hospital for Nervous Diseases, London, UK). Brain infarctions were identified on $T_1$-weighted images and confirmed on the corresponding $T_2$-weighted images, with the volumetric measurements being carried out on $T_1$-weighted images. Each infarction was delineated manually to obtain its cross-sectional area on each slice to which it extended, from which the total stroke volume was computed. The volumes of gray matter, white matter and CSF were calculated after the segmentation of $T_1$-weighted MRI using SPM99. Intracranial volume (ICV) was measured as the sum of the total gray matter, white matter and CSF, and total brain volume as the sum of total gray matter and white matter. A brain atrophy index was calculated using the formula (ICV – brain volume)/ICV. White matter hyperintensities (WMHs) were identified on FLAIR sequences. A special computer program was written by one of the authors (W.W.) to automatically delineate WMHs in both the periventricular and deep white matter regions [18]. The absolute volume of total white matter and WMHs were determined, and the percentage of white matter with a hyperintense signal was calculated for each subject. The reliability and validity of this method have been described elsewhere [18].

*Consensus Diagnosis*

The diagnosis was assigned to each subject in a case conference at which all medical, psychiatric, neuropsychological and neuroimaging data were presented, and a consensus was reached. A neuropsychiatrist, a psychogeriatrician, a neurologist and one or more research psychologists attended the meeting. For dementia (VaD) diagnosis, a subject must have definite impairment in 2 or more cognitive domains (impairment in memory was not necessary), demonstrate evidence of functional decline because of the cognitive deficits, and have evidence of cerebrovascular disease on MRI or CT scan judged to be sufficient to account for cognitive impairment. For a diagnosis of VaMCI, the subject must have definite impairment in one domain, or marginal impairment in two domains or, if there was impairment in more domains, the functional decline criterion for VaD was not met. Impairment in a cognitive domain was defined as definite impairment (<5th percentile) on at least one test or marginal impairment (5th–10th percentile) on at least two tests in that domain. Functional decline was a decline in a SOFAS score of ≥20 from the pre-morbid estimate or failure on one item of ADL or two items of IADL due to cognitive deficits as judged by consensus.

## Results

*Subject Characteristics*

Of the 1,050 patients with possible stroke or TIA screened for study suitability, 252 met inclusion and exclusion criteria and were entered into the study. The major reasons for exclusion, in order of frequency, were: (a) refusal by subject or family member (n = 550); (b) lack of confirmation of diagnosis (n = 66); (c) critical medical condition (n = 53); (d) lack of competence in English (n = 44); (e) severe aphasia (n = 36); (f) pre-existing dementia clinically or based on the IQCODE score (n = 27); (g) age >87 years (n = 22); and (h) TIA (n = 35). By the time of detailed assessment at 3–6 months following the cerebrovascular event, 41 were lost to follow-up (33 withdrew, 3 died, 4 relocated outside Sydney and 1 was not contactable). One was excluded for baseline dementia missed earlier. Of the 210 patients in the study, 170 completed a detailed neuropsychological assessment, but 1 was reclassified as a patient with possible Alzheimer's disease (AD). Patients included (n = 169) were compared with potential subjects excluded (n = 916) on age and sex, and there were no significant differences. The patients with (n = 169) and without (n = 40) complete assessment were compared on age, sex, and years of education, with no significant differences noted, but those with complete assessment were non-significantly higher functioning on ADL and IADL. Subjects with (n = 101) and without

**Table 1.** The demographic and functional characteristics of the study sample

| | Control (n = 103) | Stroke cohort with neuropsychological evaluation (n = 169)[a] | NCI (n = 68; 40.2%) | VaMCI (n = 62; 36.7%) | VaD (n = 36; 21.3%) | p[b] (VaMCI + VaD vs. NCI) | p[b] (VaD vs. VaMCI) |
|---|---|---|---|---|---|---|---|
| Age, years | 71.1 (6.32) | 72.2 (9.0) | 69.6 (8.9) | 73.0 (9.4) | 74.9 (7.4) | 0.006* | 0.310 |
| Females/males (% females) | 52/103 (49.5) | 66/169 (39.1) | 21/68 (30.9) | 31/62 (50.0) | 13/36 (36.1) | 0.0728 | 0.2619 |
| Education, years | 11.7 (3.3) | 10.1 (2.6) | 10.9 (3.0) | 9.7 (2.3) | 9.4 (2.2) | 0.003* | 0.521 |
| NART-IQ | 114.1 (7.7) | 104.9 (10.5) | 110.3 (8.7) | 102.6 (9.5) | 98.1 (10.7) | <0.0001* | 0.055 |
| MMSE | 28.8 (1.4) | 27.9 (2.4) | 29.1 (1.0) | 28.0 (1.9) | 25.8 (3.4) | <0.0001* | <0.0001* |
| ADL | 5.9 (0.3) | 5.2 (1.4) | 5.8 (0.8) | 5.2 (1.4) | 4.2 (1.8) | <0.0001* | 0.004* |
| IADL | 7.1(1.4) | 6.7 (2.0) | 7.6 (1.1) | 6.9 (1.6) | 4.7 (2.4) | <0.0001* | <0.0001* |
| IQCODE | 49.3 (2.0) | 50.0 (4.1) | 49.7 (3.3) | 48.7 (1.4) | 52.6 (6.9) | 0.719 | 0.044* |
| SOFAS | 90.2 (5.3) | 80.5 (12.4) | 86.9 (8.6) | 80.8 (9.8) | 68.5 (13.5) | <0.0001* | <0.0001* |

The assessment was 3–6 months after index stroke or TIA. The IQCODE measured decline in 5 years prior to the stroke. * Significant ($p < 0.05$) values.

NCI = No cognitive impairment; NART-IQ = National Adult Reading Test – Intelligence Quotient [32]; MMSE = Mini-Mental State Examination [9]; ADL = Activities of Daily Living [33]; IADL = Instrumental Activities of Daily Living [34]; IQCODE = Informant Questionnaire for Cognitive Decline in the Elderly [7]; SOFAS = Social and Occupational Functioning Assessment Scale [20].

[a] Three subjects were excluded because of diagnosis of AD, 2 in combination with VaD.

[b] All tests controlled for multiple comparisons. Bonferroni correction was used.

(n = 68) MRI scans were compared on age, years of education and sex, and no significant differences were noted. The controls (n = 103) were well matched with the subjects on age, but had a greater proportion of women and higher education. Both of these factors were corrected for in the analyses (table 1).

*Clinical Features*

One hundred and fifty-eight patients had a completed stroke and 11 had a TIA. Stroke subjects had a mean age of 72.2 (SD 9.0) years and 60.1% were men. The numbers in the age bands 50–60, 61–70, 71–80 and 81–90 years were 23, 38, 79 and 25, respectively. The demographic and functional indices of the VaD, VaMCI and non-dementia subjects are presented in table 1, and the putative cerebrovascular risk factors in table 2. The characteristics of the strokes and TIAs are presented in table 3. When the MRI scans were carefully analysed, 76.0% of patients had brain infarcts, which were large infarcts in 32.3% (right-sided n = 23, left-sided n = 8) and lacunar infarcts in 43.7%. In the patients with lacunar infarcts, the mean number was 2 (range 1–6), and in those with large infarcts, the mean was 1.8 (range 1–5). The mean volume of lacunar infarcts was 0.59 ml, and that of large infarcts was 6.4 ml.

*Prevalence of Impairment*

Thirty-six (21.3%) subjects were diagnosed as VaD by consensus, 1 as AD and 2 with mixed AD and VaD. One subject in the age range 50–60 years was diagnosed with VaD, whereas 24% in the 61–70 years, 23% in the 71–80 years, and 32% in the >80 years age group had this diagnosis ($\chi^2 = 5.03$, $p = 0.025$). The prevalence of VaMCI was 36.7%, such that altogether 58.0% patients had significant cognitive impairment.

*Comparison of Impaired with Non-Impaired Subjects*

Impaired subjects, those with VaD or VaMCI, were older but there were no sex differences in the two groups. They had 1.3 years less education and a lower NART-IQ score than the non-impaired subjects (table 1). The two groups did not differ on any particular cerebrovascular risk factor except that impaired patients had a higher overall number of risk factors in comparison to non-impaired patients ($p = 0.026$). The two groups did not differ on the side of stroke, whether the strokes involved the cerebral hemisphere or brain stem/cerebellum, and large or lacunar strokes. The proportion of stroke and TIA subjects with a history of previous stroke or TIA did not differ in the two groups. VaD subjects had a slightly but significantly higher score on the ESS, indicating greater disability.

**Table 2.** The cerebrovascular risk factors for the dementia and non-dementia groups in the stroke cohort with neuropsychological evaluation

| Risk factors | Stroke cohort % (n) | NCI % (n) | VaMCI % (n) | VaD % (n) | p (VaMCI + VaD vs. NCI) | p (VaD vs. VaMCI) |
|---|---|---|---|---|---|---|
| Hypertension | 55.6 (94/169) | 55.9 (38/68) | 56.5 (35/62) | 55.6 (20/36) | 0.9239 | 0.8632 |
| Cholesterolemia | 33.7 (57/169) | 32.4 (22/68) | 40.3 (25/62) | 25.0 (9/36) | 0.4135 | 0.1881 |
| Smoker | 50.9 (86/169) | 51.5 (35/68) | 45.2 (28/62) | 55.6 (20/36) | 0.8746 | 0.4338 |
| Diabetes mellitus | 14.2 (24/169) | 11.8 (8/68) | 12.9 (8/62) | 16.7 (6/36) | 0.8116 | 0.8307 |
| Previous TIA | 18.3 (31/169) | 11.8 (8/68) | 22.6 (14/62) | 25.0 (9/36) | 0.0890 | 0.9799 |
| Previous stroke | 11.8 (20/169) | 14.7 (10/68) | 6.5 (4/62) | 16.7 (6/36) | 0.5262 | 0.2061 |
| Previous AMI | 16.6 (28/169) | 17.6 (12/68) | 17.7 (11/62) | 13.9 (5/36) | 0.5975 | 0.8825 |
| Previous angina | 19.5 (33/169) | 17.6 (12/68) | 21.0 (13/62) | 19.4 (7/36) | 0.9308 | 0.8569 |
| Atrial fibrillation | 23.1 (39/169) | 16.2 (11/68) | 22.6 (14/62) | 33.3 (12/36) | 0.3795 | 0.3550 |
| Mean (SD) CVRF score | 2.5 (1.4) | 2.2 (1.4) | 2.6 (1.5) | 2.8 (1.4) | 0.026* | 0.727 |

The Cardiovascular Risk Factor (CVRF) score is the sum of 9 risk factors listed above (range 0–9). * $p < 0.05$.
NCI = No cognitive impairment; TIA = transient ischemic attack; AMI = acute myocardial infarction.

**Table 3.** Clinical and MRI brain characteristics of the sample

| | Healthy controls (n = 103) | NCI (n = 68) | VaMCI (n = 62) | VaD (n = 36) | p (VaMCI + VaD vs. NCI) |
|---|---|---|---|---|---|
| Clinical stroke | | | | | |
| Laterality (right sided) | – | 42.6 (29/68) | 54.8 (34/62) | 47.2 (17/36) | 0.3015 |
| Lacunar infarct | – | 32.4 (22/68) | 25.8 (16/62) | 22.2 (8/36) | 0.3489 |
| Prior CVA | – | 14.7 (10/68) | 6.5 (4/62) | 16.7 (6/36) | 0.5262 |
| Depression | | | | | |
| Hamilton Rating Scale | 1.4 (1.6) | 2.9 (3.3) | 3.9 (5.4) | 2.8 (3.5) | 0.507 |
| Geriatric Depression Scale | 1.9 (2.4) | 1.73 (2.3) | 2.9 (2.4) | 3.6 (2.6) | 0.001* |
| Brain MRI | | | | | |
| Whole Brain Atrophy score | 1.0 (1.2) | 1.6 (1.8) | 1.5 (1.8) | 1.6 (1.2) | 0.989 |
| Infarct volume, $mm^3$ | – | 1,643.2 (8,214.4) | 933.1 (1,664.8) | 7,276.9 (12,370.1) | 0.405 |
| Infarcts | – | 1.0 (1.3) | 1.9 (1.4) | 1.3 (1.0) | 0.008* |
| Total WMH | 5.4 (2.8) | 6.4 (3.0) | 8.2 (4.1) | 9.5 (4.0) | 0.004* |
| Periventricular WMH | 3.3 (1.0) | 3.4 (1.1) | 4.0 (1.5) | 4.3 (1.3) | 0.008* |
| Homocysteine | 13.0 (4.4) | 16.8 (6.0) | 18.6 (7.4) | 16.6 (8.0) | 0.537 |

The stroke characteristics are presented as percentages. Values for the depression and MRI features as well as homocysteine are expressed as mean (SD). * $p < 0.05$. NCI = No cognitive impairment; WMH = white matter hyperintensities rating.

*Comparison of VaMCI with VAD*

The VaMCI group did not differ from VaD on age, sex, education and NART-IQ but, as expected, the VaMCI had higher scores on the MMSE, ADL, IADL and SOFAS. Cerebrovascular risk factors and their numbers were similar in the two groups (table 2).

*Determinants of VaD*

The first logistic regression incorporated 5 independent variables: age (odds ratio, OR, 1.06, CI 1.003–1.121, $p = 0.039$) was a significant predictor, but education (OR 0.9, CI 0.75–1.08), sex (OR 1.7, CI 0.69–4.78) and CVRF score (OR 1.18, CI 0.89–1.57) were not significant. The second regression analysis had 5 stroke-related variables: the ESS score was significant (OR 0.94, CI 0.88–0.99, $p = 0.03$), but not the other variables which were lateral-

ity of stroke (OR 1.008, CI 0.46–2.195), cerebral hemispheric or non-hemispheric stroke (OR 0.82, CI 0.39–1.69), lacunar or large stroke (OR 0.57, CI 0.72–6.34), and previous stroke or TIA (OR 2.13, CI 0.72–6.34). The third regression analysis examined 3 variables, two of which were significant: NART-IQ (OR 0.92, CI 0.88–0.96, $p < 0.0001$) and IQCODE for previous 5 years (OR 1.29, CI 1.03–1.61, $p = 0.03$). The category depression (Hamilton Depression Rating Scale score >10 or GDS score >5) was not significant (OR = 1.34, CI 0.117–15.335). In the fourth analysis, homocysteine was examined and was non-significant (OR = 0.98, CI 0.90–1.06). The fifth analysis examined four MRI variables, with one being significant: total infarct volume (OR 1.71, 1.183–2.49, $p = 0.004$). The non-significant variables were: brain atrophy index (OR 0.94, CI 0.61–1.46), number of infarcts (OR 0.75, CI 0.38–1.46), and WMH score (OR 1.13, CI 0.95–1.35).

When significant variables from the above analyses were entered into a final logistic regression analysis, only infarct volume (OR 1.95, CI 1.25–3.04, $p = 0.003$) and IQCODE (OR 2.55, CI 1.20–5.42, $p = 0.015$) were significant.

*Determinants of VaMCI*

The logistic regression analyses were repeated to examine determinants of VaMCI in contrast with no cognitive impairment. The only significant variable was NART-IQ (OR 0.875, CI 0.797–0.96, $p = 0.005$).

## Discussion

We report a prevalence rate of VaD of 21.3% in a well-characterised cohort of stroke subjects examined 3–6 months after the index event. All cases of VaD, bar one, were diagnosed in those over 60 years. Our figures are consistent with previous reports, with one previous study [1, 19] reporting a rate of 26.4% in individuals aged 60–90 years, and another study [2] reporting a rate of 25% in individuals 55–85 years old. Age was a significant determinant of prevalence in our Sydney Stroke Study only when we used 60 years as the cut-off, i.e. the prevalence rate did not increase after the age of 60 years. In the New York study, subjects in their 60s had a lower rate than those 70 years and older. When age was entered into logistic regression along with other possible determinants of dementia, it was no longer significant. This is possibly because age is correlated with cerebrovascular risk factors as well as brain imaging parameters such as atrophy and WMHs. It can be concluded that a stroke in an older person is more likely to produce dementia than in someone <60 years. This is considered to be due to the additional cerebrovascular pathology in older brains, which may be due to previous infarctions and non-infarct ischaemic changes. The role of Alzheimer-type pathology in older brains is another important factor, with post mortem examination necessary to determine its relative contribution.

The prevalence rate of VaD in this study compares well with other hospital-based populations [1, 2, 19] even though the definition of dementia used in our study was different, an issue discussed below. The rates of the hospital-based studies are much higher than the rate reported from the Framingham Study in which subjects who had been examined prior to the stroke were followed up for 10 years after the stroke [3]. The rate of dementia was 19.3% in stroke patients compared to 11.0% in controls, suggesting a twofold increase in risk of stroke over a 10-year period in the community-based sample [3]. This compares with a ninefold increase reported in a cross-sectional study immediately following stroke [19]. It is possible that strokes in the community sample were less severe. The DSM-IV [20] criteria used in this study may also have played a role as they are insensitive to subcortical dementia. The subjects in the Framingham Study were selected for their lack of dementia at baseline, which was made possible by the longitudinal design. In our cross-sectional study, we attempted to do this by retrospective assessment using the IQCODE, an informant-based assessment of cognitive decline prior to the stroke. We excluded 27 subjects primarily on this criterion. In spite of this exclusion, IQCODE score remained a weak predictor of dementia diagnosis, and it is likely that in other studies that did not have such exclusion, the contribution of pre-existing pathology was greater. Previous studies have shown that pre-existing cognitive deficits are common in this sample [2, 21], and post-stroke dementia should not be considered to be new onset dementia.

The definition of VaD used is an important consideration in the interpretation of prevalence rates. The construct of VaD is still evolving and the currently available criteria sets have low correspondence with each other [22, 23]. The criteria used in our study differed from those used in other studies in that memory impairment was not necessary and deficits in any two cognitive domains were sufficient. This is similar to the ADDTC criteria [24] but different from the DSM-IV [20] and NINDS-AIREN criteria [25]. Unlike the ADDTC criteria, however, the presence of two or more ischaemic strokes or one or more

infarcts on CT or $T_1$-weighted MRI was not necessary, and extensive white matter disease was sufficient for the diagnosis. Another feature of our diagnoses was that the neuropsychological and functional criteria were operationalised, and the significance of the vascular pathology was based on CT or MRI scans. MRI scans were available for the majority and post-stroke CT scans for all patients. However, the decision whether the vascular pathology on brain scans was sufficient to account for the cognitive impairment was based on 'clinical judgement' of the consensus group. This group comprised a neuropsychiatrist, a neurologist, a psychogeriatrician and at least one neuropsychologist, who engaged in discussion before making the decision. The presence of an infarct was not considered necessary if the subject had extensive white matter pathology, although most subjects had a combination of the two kinds of lesions. Furthermore, memory impairment was not an essential criterion for the diagnosis of impairment or dementia. Applying the memory impairment criterion to our definition of dementia would have changed the prevalence considerably. Nine (25%) of the dementia subjects did not have marginal or definite memory impairment in either verbal or non-verbal domain, and would not have met the DSM-IV or the NINDS-AIREN criteria. Twenty-six (72.2%) of VaD subjects did not have definite verbal memory impairment in our sample.

The Sydney Stroke Study is noteworthy for also reporting the prevalence of MCI in this sample, presumably again of vascular origin. More than one third of stroke subjects met our criteria for MCI, and the combined VaD and VaMCI groups accounted for nearly 60% of the sample. This suggests that the majority of stroke subjects have cognitive impairment, with about a quarter reaching the threshold for dementia diagnosis. We were interested in knowing whether the determinants for dementia were qualitatively or quantitatively different from those for VaMCI.

Previous studies have identified some stroke-related factors as determinants of dementia, in particular lacunar infarcts, left-sided lesions and hemispheric infarcts [1, 2]. A major dominant stroke syndrome and dysphasia have also been related to dementia [2, 26]. These findings have, however, not been consistent, with other studies failing to support these relationships [27], including our own. Since our study necessitated a demanding assessment schedule, it is likely that many severely ill subjects were excluded. We also excluded subjects with severe aphasia or non-fluency in English because of the difficulty in obtaining informed consent and assessing neuropsychological function. This may have contributed to the lack of a left-hemispheric bias in our dementia subjects. Hypertension, diabetes [27], atrial fibrillation [28, 29] and other recognised cerebrovascular risk factors have emerged as independent risk factors for dementia in some studies but not others. In the Framingham Study, after stroke had been accounted for, exposure to individual risk factors did not alter the hazard ratio. Our preliminary analysis did suggest that overall cerebrovascular risk factor exposure was associated with cognitive impairment, but it was not significant in the combined regression analysis.

The brain imaging parameters we examined were atrophy, volume of infarction, number of infarcts and WMHs, of which only total stoke volume was significant (OR 1.71). Brain atrophy in this study, being measured after the stroke, does not accurately reflect baseline atrophy since it is confounded by the stroke itself. We had hypothesised that stroke volume *and* number would be independent predictors of dementia, and this was only partially borne out. About 70% of our subjects had this event as the first clinical stroke, and the multiple infarcts seen in many subjects were lacunar and small in volume. Such subjects were more likely to have extensive WMHs. That we found WMHs to be greater in those with cognitive impairment is consistent with some previous reports [2, 27] and the literature reporting a relationship between WMHs and cognitive impairment [8]. It also reflects the definition of VaD we used: the presence of an infarct was not necessary if extensive WMHs were present on MRI, and deficits in any two cognitive domains were sufficient for the diagnosis without memory being specifically affected. MRI scans were not always available on our subjects. In such cases, CT scans were used to assess white matter disease. The threshold for significant white matter lesions was therefore high and WMHs on $T_2$-weighted FLAIR imaging were considered clinically significant if abnormality was also seen on CT scans.

Some other factors that were non-significant must be commented upon. Depression was not significantly different in the two groups. It is noteworthy that in those with depression, the neuropsychological assessment was postponed until remission had occurred. Also noteworthy is that homocysteine did not emerge as a risk factor in this study. Homocysteine has a complex relationship with vascular cognitive impairment as it has been implicated as a risk factor for stroke, microvascular disease, and Alzheimer's disease and may be directly neurotoxic [30, 31].

The study had a number of limitations. Firstly, this is a cross-sectional study with subjects being assessed only

after the stroke had occurred. In spite of our exclusion of subjects with baseline cognitive impairment prior to stroke, we cannot be certain that subjects with mild cognitive impairment on the basis of Alzheimer-type pathology did not enter the study. Secondly, a large proportion of subjects were excluded for various reasons, but we do not consider it to have introduced a systematic bias in our sample based on our analysis of the minimal data available on those excluded. However, the more severely affected patients were likely to be excluded. The prevalence rates were possibly underestimated by this study for this reason. Thirdly, not all subjects had an MRI scan, thereby reducing the power of detecting differences in neuroimaging parameters. Fourthly, genetics data were not available, and therefore the contribution of apolipoprotein E polymorphism to the diagnostic status could not be examined.

In conclusion, our study supports the high prevalence of dementia and mild cognitive impairment following stroke, especially in older individuals, and highlights the importance of cognitive reserve. Both infarction and non-infarct ischaemic lesions make a contribution to dementia, and the contribution of cerebrovascular risk factors is not independent of the stroke risk. Stroke volume is a significant determinant of post-stroke dementia.


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