Neuropsychological Predictors of Incident Dementia in Patients With Vascular Cognitive Impairment, Without Dementia

Janet L. Ingles, PhD; Carolyn Wentzel, PhD; John D. Fisk, PhD; Kenneth Rockwood, MD

Background—Vascular cognitive impairment that does not fulfill dementia criteria (ie, vascular cognitive impairment, no dementia [CIND]) is common. Although progression to dementia is frequent, little is known about factors that predict progression. We examined whether performance on neuropsychological tests administered at baseline could predict incident cases of dementia in patients with vascular CIND after 5 years.

Summary of Report—The Canadian Study of Health and Aging is a prospective, cohort study of 10 263 randomly selected persons aged ≥65 years. Of 149 people diagnosed with vascular CIND, 125 completed a battery of neuropsychological tests at baseline. Follow-up cognitive diagnoses were available for 102 individuals. After 5 years, 45 patients (44%) developed dementia. Low baseline scores on tests of memory and category fluency were associated with incident dementia.

Conclusions—Neuropsychological measures can indicate risk of dementia in patients with vascular CIND. This study did not suggest a prediction-to-progression profile distinct from that seen in Alzheimer disease. (Stroke. 2002;33:1999-2002.)

Key Words: cerebrovascular disorders ■ dementia ■ neuropsychology

Vascular cognitive impairment (VCI) forms a spectrum that includes vascular dementia (VaD), Alzheimer disease (AD) with a vascular component (referred to as mixed AD), and vascular cognitive impairment that does not meet dementia criteria (referred to as vascular cognitive impairment, no dementia [CIND]). In the vascular CIND subtype, dementia may be excluded because the cognitive impairment is focal and/or memory is relatively spared or because it is not sufficiently severe to cause functional impairment.

In the Canadian Study of Health and Aging (CSHA), vascular CIND was the most prevalent form of VCI (2.6% for those aged ≥65 years) and conferred an increased risk of death and institutionalization. Within 5 years, approximately half of this group progressed to dementia, although no clinical or demographic factors other than sex (women were at greater risk) predicted progression to dementia. However, the role of neuropsychological variables, which have been useful in predicting the development of AD from mild cognitive impairment, has not yet been considered.

We examined whether performance on neuropsychological tests administered at baseline could predict incident cases of dementia in this vascular CIND group. Specifically, we were interested in whether the incident dementia cases displayed the “frontal-subcortical” pattern characteristic of vascular dementia or the “temporal-neocortical” pattern characteristic of AD.

Subjects and Methods

The CSHA is a prospective, cohort study of 10 263 randomly selected community- and institutional-dwelling persons, aged ≥65 years. In 1991–1992, all institutional participants and community participants who scored <78 of 100 on the Modified Mini-Mental State (3MS) examination received a clinical assessment (n=2914). Participants were diagnosed with vascular CIND if they met the following criteria: (1) they had cognitive impairment that did not meet the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) criteria for dementia (ie, they did not have both memory impairment and other cognitive impairment that caused functional deficits), and (2) their cognitive impairment was judged to have a vascular cause (eg, by evidence of sudden onset, stepwise progression, patchy cortical deficits on cognitive testing, other evidence of atherosclerosis, focal neurological findings, or neuroimaging data when available; data on vascular risk factors were available, as was the Hachinski Ischemia Score, but no Ischemia Score cut point was identified a priori, and the presence of vascular risk factors alone was insufficient for a VCI diagnosis; rather, signs of ischemia/infarction were required). All participants deemed to be testable (3MS score ≥50 of 100) were asked to complete a neuropsychological test battery as a component of the clinical assessment. Information concerning functional ability was obtained from a knowledgeable informant with the use of section H of the Cambridge Examination for Mental Disorders of the Elderly. Global functional impairment was defined as having difficulty in any 2 of the following domains: performing household chores, managing money, feeding self, dressing, and incontinence. In 1996–1997, follow-up data were collected, and surviving participants were reassessed. Dementia was diagnosed with the use of DSM-III-R criteria, with etiologic diagnoses based on National Institute of...
Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD\textsuperscript{13} and International Statistical Classification of Diseases, 10th Revision (ICD-10) criteria for VaD.\textsuperscript{14} Both criteria were used to define mixed AD. In nonsurvivors, dementia was diagnosed with the use of antemortem estimates of cognitive status from decedent interviews conducted with family members.\textsuperscript{15} These estimates have yielded high sensitivity (82\%) and specificity (93\%) values relative to CSHA clinical examination.\textsuperscript{16}

The neuropsychological test battery was selected to assess the constructs described in the DSM-III-R criteria for dementia and has been described in detail elsewhere.\textsuperscript{16} Short- and long-term memory were assessed with the Benton Visual Retention Test,\textsuperscript{17} Buschke’s Cued Recall Test (BCRT),\textsuperscript{18,19} Digit Span,\textsuperscript{20} Rey Auditory Verbal Learning Test,\textsuperscript{21–23} and the Wechsler Memory Scale Information subtest.\textsuperscript{20} Abstract thinking was assessed with the Wechsler Adult Intelligence Scale, Revised (WAIS-R) Similarities subtest.\textsuperscript{24,25} Judgment was assessed with the WAIS-R Comprehension subtest.\textsuperscript{24,25} Other higher cortical functions were assessed with the Token Test,\textsuperscript{26} Controlled Oral Word Association Test,\textsuperscript{27} Animal Naming,\textsuperscript{28} WAIS-R Digit Symbol subtest,\textsuperscript{24} visual identification of items from the BCRT,\textsuperscript{18,19} and WAIS-R Block Design subtest.\textsuperscript{24,25}

ANCOVAs, with age and education as covariates, were conducted to examine differences in baseline neuropsychological test scores between the incident dementia and no-dementia groups. Logistic regression analyses, with age, sex, and years of education as covariates, were conducted to determine the utility of the neuropsychological variables in predicting outcomes (ie, incident dementia versus no-dementia). To facilitate comparisons between the neuropsychological variables, raw scores were transformed into Z scores. In all analyses, the neuropsychological test scores were treated as continuous variables.

**Results**

At baseline, 149 participants were diagnosed with vascular CIND, of whom 125 completed the neuropsychological test battery. Fourteen participants were not administered the neuropsychological assessment because they scored <50 of 100 on the 3MS test. Ten participants refused or were unable to complete neuropsychological testing (eg, because of deafness). The participants who completed neuropsychological testing (n = 125) had higher 3MS scores than those who did not complete testing (n = 24; 77.1 versus 38.3; P < .001). However, other baseline characteristics were similar between those who completed testing (age, 79.3 years; education, 8.4 years; 63\% women; Hachinski Ischemic Score 6.2 ± 3.2) and those who did not (age, 78.9 years; education, 8.1 years; 50\% women; Hachinski Ischemia Score 7.2 ± 3.7; P > .20 for all comparisons).

Of the 125 participants who completed neuropsychological testing, follow-up cognitive diagnoses were available for 102 participants, either from clinical examination (n = 50) or antemortem estimates of cognitive status (n = 52). Participants who were diagnosed from clinical examination were younger (78.2 versus 81.2 years; P < .02), had higher 3MS scores (78.5 versus 74.6; P < .05), and included more women (74\% versus 46\%; P < .04) than those diagnosed from antemortem estimates. However, there was no difference in education level between the 2 groups (8.5 versus 8.2 years; P > .70). Of the 23 participants for whom follow-up cognitive diagnoses were not available, 6 participants refused the follow-up assessment. Nine participants were deceased, and antemortem data were not able to be collected. In the remaining 8 participants, the reasons for missing follow-up data were not able to be determined. Baseline characteristics were similar between those with available follow-up diagnoses (n = 102; age, 79.7 years; education, 8.4 years; 64\% women; 3MS = 76.5) and those without (n = 23; age, 77.4 years; education, 8.5 years; 61\% women; 3MS = 79.7; P > .10 for all comparisons).

Of the 102 participants who constituted our sample, 56\% (n = 57) were excluded from a baseline diagnosis of dementia because their functional abilities were relatively spared despite significant memory impairment. Twenty percent (n = 21) lacked both functional and memory impairment but had other cognitive impairment, while 19\% (n = 19) had both functional and memory impairment but lacked other cognitive impairment. Only 5\% (n = 5) had functional impairment in the absence of memory impairment.

Forty-four percent (n = 45) of our sample had progressed to dementia within 5 years. Of those who progressed and were alive at follow-up, 43\% (n = 10) were diagnosed with VaD, 35\% (n = 8) with AD, 13\% (n = 3) with mixed AD, and 9\% (n = 2) with unclassified dementia. Etiologic diagnoses were not available from the antemortem estimates. The incident dementia group was marginally older (81.0 versus 78.7 years; P < .07), had more women (75.6 versus 54.4\%; P < .03), and had lower 3MS scores (74.2 versus 78.3; P < .03) than the no-dementia group. The 2 groups did not differ in years of education (8.0 versus 8.6 years; P > .40). The highest rate of progression to dementia was found in those participants who had both functional and memory impairment at baseline but were excluded from a diagnosis of dementia because they lacked other cognitive impairment (58\%; 11/19). The progression rates were similar between those with memory impairment but not functional impairment (40\%; 23/57), those with other cognitive impairment but not memory or functional impairment (43\%; 9/21), and those with functional impairment without memory impairment (40\%; 2/5).

The incident dementia group performed worse than the no-dementia group on Animal Naming (9.2 versus 11.1; P < .04) and on both the free (23.7 versus 28.0; P < .05) and cued recall (total recalled on cued recall trials/total number of cues provided: 0.89 versus 0.96; P < .03) components of the BCRT. Performance of the 2 groups did not differ on any other neuropsychological measures. Considered individually, low baseline scores on the free and cued BCRT and on Animal Naming each had a similar association with incident dementia; however, only the cued BCRT was statistically significant (Table). Individual entries of the neuropsychological variables resulted in similar sensitivity and specificity estimates. The estimates also did not change substantially when the 3 variables were entered together or in pairwise

**Results of Individual Logistic Regression Analyses Predicting Incident Dementia With Age, Sex, and Years of Education as Covariates**

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free BCRT</td>
<td>1.57</td>
<td>0.98–2.50</td>
<td>0.06</td>
<td>44.4</td>
<td>75.4</td>
</tr>
<tr>
<td>Cued BCRT</td>
<td>1.64</td>
<td>1.00–2.68</td>
<td>0.05</td>
<td>46.7</td>
<td>79.0</td>
</tr>
<tr>
<td>Animal Naming</td>
<td>1.64</td>
<td>0.98–2.73</td>
<td>0.06</td>
<td>45.2</td>
<td>78.6</td>
</tr>
</tbody>
</table>
combinations, likely because of their high intercorrelations. It is important to note that even among those patients with overt memory impairment at baseline (n=76; i.e., those excluded from a diagnosis of dementia because of lack of functional impairment or other cognitive impairment), the incident dementia group (n=34) performed worse than the no-dementia group (n=42) on the free (21.9 versus 26.1; P<0.02) and cued (0.87 versus 0.95; P<0.02) BCRT, suggesting that it is the relative severity of memory deficits that predicts progression to dementia.

**Discussion**

The advantage of the VCI construct, over that of traditional VaD, is that it allows for inclusion of patients with cognitive impairment who do not meet criteria for dementia. This vascular CIND diagnosis confers an increased risk of death and institutionalization and progresses to dementia in approximately half of the cases. In this representative cohort study, we found that the incident dementia cases performed significantly worse at baseline on tests of memory (i.e., free and cued BCRT) and category fluency (i.e., Animal Naming) than those who did not develop dementia. Each of these neuropsychological variables contributed to the predictive model for dementia, albeit individually, with only fair sensitivity and specificity values. Measurement of these neuropsychological variables, as well as their consideration in combination, might represent a strategy by which those appropriate for preventative efforts can be identified.

Cognitive impairment in the incident dementia group did not conform to the frontal-subcortical pattern characteristic of vascular dementia. Instead, the relative impairment on tests of memory and category fluency in the incident dementia group was more consistent with the temporal-neocortical pattern characteristic of AD. Perhaps these results are not surprising, given that almost half of the surviving cases who progressed to dementia were diagnosed with AD or mixed AD at follow-up. It should be noted, however, that in the neuroimaging literature, both letter and category fluency tasks have been found to activate left prefrontal areas, although category fluency also activates left temporal structures in general accordace with our results.

The relative severity of memory deficits predicted progression to dementia even among those patients who had overt memory impairments at baseline but were excluded from a diagnosis of dementia either because they lacked functional impairment or other cognitive impairment. This suggests that our findings do not simply reflect the progression of preclinical memory deficits at baseline to overt memory deficits at follow-up that are required by definition for a diagnosis of dementia. That is, the preclinical AD profile appears to be a true marker of the progression to dementia and not merely a definitional artifact.

Our results must be interpreted with caution given that baseline neuropsychological data were not available for all patients with vascular CIND. However, although the participants who completed neuropsychological testing had higher 3MS scores than those who did not complete testing, this latter group did not appear to be at substantially greater risk of progressing to dementia. The rate of progression to dementia in our patients who completed neuropsychological testing (44%) was comparable to that obtained previously for the entire sample of vascular CIND patients (46%). An additional limitation of our study is that follow-up cognitive diagnoses were not available for all participants. Nonetheless, after 5 years almost all patients were accounted for, and the diagnosis of dementia with the use of antemortem estimates of cognitive status from decedent interviews represents a significant methodological improvement over many previous epidemiological studies. Another weakness is that neuroimaging data were not routinely available, and diagnosis of vascular CIND at baseline relied on examination of clinical features. A final limitation of our study is that the neuropsychological test battery may not have been optimal for detecting subtle deficits of frontal-subcortical function. Although the battery included tests of abstract thinking (i.e., WAIS-R Similarities subtest), judgment (i.e., WAIS-R Comprehension subtest), verbal fluency (i.e., Controlled Oral Word Association Test), and psychomotor speed (i.e., WAIS-R Digit-Symbol subtest), other tests of executive system function (e.g., Trail Making, Card Sorting) were not included. The importance of identifying executive system dysfunction in dementia and the difficulties in assessing this construct have received increased attention recently.

Thus, prospective follow-up of larger samples, with standardized neuroimaging protocols and with better specification of measures that are sensitive to frontal-subcortical functions, will be important in the pursuit of a better understanding of the outcomes of VCI.

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**References**

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