Cognitive Functioning in Preclinical Vascular Dementia
A 6-Year Follow-Up

Erika Jonsson Laukka, MSc; Sari Jones, MSc; Laura Fratiglioni, MD, PhD; Lars Bäckman, PhD

Background and Purpose—Recent studies have shown that cognitive deficits are present during the years preceding a diagnosis of vascular dementia (VaD). The aims of this study were to (1) extend previous research by examining whether cognitive deficits are already present 6 years before diagnosis, and (2) examine the strength of the association between cognitive performance and a future VaD diagnosis after controlling for previous vascular disorders.

Methods—Subjects from a population-based study of very old persons (≥75) were examined with a test of global cognitive functioning (the Mini-Mental State Examination [MMSE]) at 3 occasions over a 6-year period. The study sample was nonrandomized. The first 2 measurement times. On the last occasion, 22 individuals were diagnosed with VaD, and 450 persons remained nondemented.

Results—The preclinical VaD group showed no MMSE deficits 6 years before diagnosis (P>0.10) compared with the controls. However, 3 years before diagnosis, poor cognitive performance was significantly associated with forthcoming VaD after controlling for demographic factors and prior vascular disorders (odds ratio, 2.55; 95% CI, 1.67 to 3.89).

Conclusions—This study extends previous findings on preclinical cognitive deficits in VaD and suggests that cognitive measures can be useful in the process of recognizing individuals at risk for developing VaD to initiate early treatment. (Stroke. 2004;35:1805-1809.)

Key Words: vascular diseases ■ dementia ■ cognitive disorders

Vascular dementia (VaD) is preceded by several years of exposure to vascular risk factors that, in the case of poststroke dementia, manifests eventually as 1 or several strokes that result in a dementia diagnosis. Management of vascular risk factors for stroke, such as hypertension, diabetes, and atrial fibrillation, would thus beneficially affect VaD occurrence. Another preventive strategy would be to detect individuals in a very early phase of VaD to initiate secondary prevention. Thus, early identification of persons at risk for VaD is important to prevent or delay dementia onset.

It is well known that Alzheimer’s disease (AD) is preceded by a preclinical phase during which cognitive deficits are detectable. A more recent observation is that cognitive deficits may be present during the years before a VaD diagnosis. In 2 previous studies, we found deficits in global cognitive functioning, as measured by the Mini-Mental State Examination (MMSE), as well as in episodic memory in persons who developed VaD 3 years later compared with normal controls. Relatedly, using the MMSE, Meyer et al observed deficits and a faster decline during the following 6 months in a group of cognitively impaired persons who developed VaD an average of 4 years later compared with a group with stable cognitive impairment. Ingles et al found that worse episodic memory and category fluency performance predicted dementia incidence within 5 years in a group classified with vascular cognitive impairment, no dementia (CIND). Thus, in addition to risk factors such as old age and various vascular conditions, degree of cognitive impairment may be predictive of future VaD.

The purpose of this study was to extend previous research by examining potential cognitive deficits 6 years before a VaD diagnosis. Of chief interest was to examine the association between MMSE performance and a future VaD diagnosis after controlling for previous vascular disorders.

Methods

Participants
Subjects were selected from participants in the Kungsholmen Project, a longitudinal population-based study that has been described in detail previously. The original population included all inhabitants in the Kungsholmen parish of Stockholm, Sweden, ≥75 years on October 1, 1987 (n=2368). At baseline, a dementia-free cohort (n=1475) was identified by means of a 2-phase study design. Persons who refused participation (or had moved to a different area) at baseline assessment (n=377) were not different from participants with regard to age and sex. All participants were invited back for follow-up assessments ~3 and 6 years later. Persons from the dementia-free cohort who refused participation at first follow-up (n=172) were younger but had similar sex distribution and MMSE scores to the participants. Only 46 (6%) of those who were nondemented at first follow-up refused participation at second...
follow-up. These persons did not differ from the participants in age, sex distribution, or MMSE performance.

Dementia diagnosis was made in 3 steps according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition-revised (DSM-III-R).13 First, the examining physician made a preliminary diagnosis. Second, an independent preliminary diagnosis was made on the basis of computerized data only. In cases of disagreement, a supervising physician made the final diagnosis. For subjects who died before follow-up examination, dementia diagnosis was based on clinical records, discharge diagnoses, and death certificates.

Differential diagnosis between AD and VaD was based on clinical data with support of the Hachinski Ischemic Scale.14 Because brain imaging or neuropathological examinations could not be performed, the majority (82%) of subjects diagnosed with VaD had a history of stroke related in time to the onset of dementia symptoms. Thus, the VaD diagnosis was of poststroke (strategic or multi-infarct) dementia. The criteria used for VaD correspond closely to the possible VaD category according to National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences criteria.13

All subjects in this study were nondemented at baseline and first follow-up assessment. At second follow-up, 22 persons were diagnosed with VaD and were assigned to the incident VaD group. The controls were selected from those persons who were nondemented at baseline. From these, we excluded persons who developed dementia during the follow-up period (n = 309) and those for whom diagnostic information at follow-up was missing because the person had died (n = 494), moved (n = 32), or refused further participation (n = 181).

Both samples were screened for severe psychiatric disorders and Parkinson’s disease, resulting in the exclusion of 4 control persons, leaving 455 persons in this group.

Baseline characteristics of incident VaD persons and normal controls are presented in Table 1. The incident VaD group was older than the controls (F(1,459) = 8.24; P < 0.01), although there were no group differences with regard to education (F < 1) or sex distribution (χ² [1; n = 477] = 0.21 [P > 0.60]). Mean follow-up interval for all subjects was 3.43 years (SD = 0.53) between baseline and first follow-up, and 3.27 years (SD = 0.48) between first and second follow-up.

### Cognitive Measure

The MMSE11 consists of 11 subscales (maximum score in parentheses) that are summarized into a total score (30): orientation to time (5), orientation to place (5), immediate word recall (3), attention (5), delayed word recall (3), naming (2), repetition (1), following commands (3), reading (1), writing (1), and design copy (1). Attention was assessed with 2 tasks, serial sevens and spelling a word backward, and the highest of the 2 scores was recorded.

### Vascular Disorders

Information on vascular disorders was derived from the Stockholm inpatient register containing admission and discharge diagnoses for all instances in which Stockholm habitants received hospital care since April 1969. The diagnoses used were hypertensive disease (International Classification of Diseases [ICD]-8:400 to 404; ICD-9:401 to 405), diabetes (ICD-8/9:250), heart disease (ICD-8/9:410 to 414, 427 to 428), and cerebrovascular disease (ICD-8/9:430 to 438).

### Results

MMSE scores for incident VaD persons and controls are presented in Table 2. A repeated-measures ANCOVA with 2 groups and 3 measurement points was conducted on the total MMSE score. For all analyses, the demographic variables served as covariates. This analysis revealed a main effect of group (F(1,459) = 89.85, P < 0.001), no effect of time (F(2,466) = 2.44, P > 0.08), and an interaction between group and time (F(2,466) = 53.14; P < 0.001). The interaction effect reflected greater decline for the incident VaD group than for the other groups.
controls during the follow-up period. Paired t tests showed that the incident VaD persons declined significantly between baseline and first follow-up (P<0.01) and between first and second follow-up (P<0.001).

A repeated-measures multivariate ANCOVA, including all MMSE subscales, also showed an overall effect of group (Wilks’ = 0.71; F11,457 = 16.98; P<0.001), no effect of time (F<1), and an interaction between group and time (Wilks’ = 0.71; F12,446 = 8.17; P<0.001). Paired t tests showed that the incident VaD group declined significantly between baseline and first follow-up on orientation to time and between first follow-up and time of diagnosis on orientation to time and place, attention, repetition, following commands, and design copy (P<0.05).

Consistent with the within-group comparisons, separate ANCOVAs showed no group differences at baseline on MMSE total (P>0.13), although the controls performed better than the incident VaD persons at first follow-up (P<0.001), with the group effect increasing greatly at time of diagnosis. Regarding the individual items, the incident VaD group showed significantly lower performance than the controls at first follow-up on orientation to time and place, attention, and delayed recall. At time of diagnosis, significant group differences were found for all subscales except reading and writing (P<0.05).

Table 3 shows the number of persons affected by vascular disorders from 1969 to baseline or first follow-up. A history of vascular disorders was nearly 3× more common among incident VaD persons compared with controls. This difference was still significant after controlling for age, sex, and education at baseline, (F1,472 = 8.20; P<0.01) and first follow-up (F1,472 = 12.54; P<0.001).

To examine the strength of the association between MMSE performance and a future VaD diagnosis, 4 logistic regression analyses were conducted with dementia status at second follow-up as the outcome variable. In all analyses, the demographic variables were entered in the first block, and then a history of vascular disorders up to the time of baseline or follow-up assessment was entered. In the final step, MMSE performance was entered, either as a total score or as 11 individual items in stepwise-forward fashion. All continuous variables were converted into z-scores to facilitate comparison of the relative importance of the variables.

Results from logistic regressions are shown in Table 4. Six years before diagnosis, a history of vascular disorders was associated with an increased risk of incident VaD, although performance on the MMSE total score was not associated with future VaD. Analogously, neither of the individual subscales was significantly associated with future VaD.

Three years before diagnosis, MMSE performance was significantly associated with an increased risk of future VaD after controlling for demographic factors and a history of vascular disorders. Interestingly, controlling for previous vascular problems did not substantially weaken the association between cognitive performance and future VaD (odds ratio after controlling only for demographic factors, 2.63; 95% CI, 1.75 to 3.95). This may reflect the fact that (1) age was already controlled for (higher age was related positively to presence of vascular disorders in both groups), and (2) a substantial proportion of the controls was also affected by vascular disease. As for the individual subscales, orientation to place was related most strongly to incident VaD 3 years before diagnosis. Regarding the individual items, the incident VaD group showed significantly lower performance than the controls at first follow-up on orientation to time and place, attention, and delayed recall. At time of diagnosis, significant group differences were found for all subscales except reading and writing (P<0.05).

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**Discussion**

The present results show that cognitive performance, as measured by the MMSE, was not significantly related to future VaD 6 years before diagnosis. However, 3 years before diagnosis, MMSE performance was associated with incident VaD. This association remained after controlling for demographic factors and a history of vascular disorders.
The individual MMSE subscales that showed significant impairment 3 years before diagnosis were orientation to time and place, delayed recall, and attention. These results are in accordance with the findings from a previous study, in which we found orientation to time and place and delayed recall to be associated with incident VaD 3 years later. The results are also consistent with the findings of Meyer et al that the subscales measuring orientation declined the most in subjects who later developed VaD. It is noteworthy that 3 of 4 subscales in which preclinical deficits were found in the present study have an episodic memory referent, whereas subscales in which preclinical deficits were found in the present study have an episodic memory referent, whereas performance on the attention subscale reflects working memory abilities. This is an interesting pattern of results because studies on AD have consistently found episodic memory functioning to be impaired preclinically. The present findings confirm previous observations that cognitive impairment might be an early sign of VaD as well as AD and provide further evidence of similarities in the pattern of cognitive deficits before diagnosis in these dementia disorders.

At time of diagnosis, the incident VaD group showed deficits on all MMSE subscales except reading and writing. This is in accordance with previous findings that relatively passive language operations are well preserved in the early clinical stages of VaD. The incident VaD group showed no MMSE impairment at baseline, after which decline was relatively rapid. However, the lack of significant cognitive deficits 6 years before diagnosis might be partly attributable to power problems because the VaD group was relatively small. Also, the rate of change from baseline to first follow-up was considerably smaller than that from first follow-up to time of diagnosis. Thus, the results of the present study are largely consistent with previous data on preclinical AD cases, indicating relative stability in cognitive performance up to ~3 years before the dementia diagnosis.

The presence of preclinical cognitive deficits in VaD likely reflects circulatory disturbances affecting brain functioning before dementia diagnosis. Several vascular conditions are known to affect cognitive functioning in nondemented elderly subjects. Long-standing hypertension may affect the media and thicken the vessel walls, impairing the capacity of small blood vessels to dilate in response to increased need for blood supply. Insufficient blood flow leads to decreased glucose metabolism, which has negative effects on cognitive functioning. Impaired autoregulation of blood flow may also contribute to development of ischemic white matter lesions. Thus, long-term hypertension may influence cognitive functioning directly by affecting brain metabolism and more indirectly by increasing the risk of structural changes. In addition to white matter lesions, clinically silent strokes have been associated with poorer cognitive functioning. It is known that many cognitive abilities draw on a widespread network of brain regions. Thus, disruption at any of the multiple sites in this network may influence cognitive performance. Therefore, silent infarctions in different brain regions may result in both global and more specific cognitive deficits.

Cognitive performance was associated with incident VaD 3 years later even after controlling for previous vascular disorders. However, impairment of cognitive performance in preclinical VaD should logically reflect alterations in brain function as a result of circulatory disturbance. Thus, with complete information on preclinical vascular changes, cognitive measures would be expected to add relatively little with regard to identification of at-risk individuals. Access to neuroimaging data on the persons in this study might have revealed white matter changes or silent strokes severe enough to affect cognitive functioning. However, it may not be realistic, even in a clinical setting, to obtain information on all vascular factors relevant to cognition and VaD. Thus, cognitive measures should still be useful for detecting persons with severe enough vascular problems to cause cognitive impairment, who have a high probability of developing VaD.

The frequency of vascular disorders reported in Table 3 likely reflects an underestimation. Because only persons who had visited a hospital were included in this category, information on vascular problems was not present for the entire sample. However, for some vascular disorders, the estimates are likely to be quite accurate. For example, in Sweden, a stroke causes hospital admission in >90% of cases. In contrast, isolated hypertension or diabetes are not conditions severe enough to require hospital care and would thus not be identified to the same extent.

A limitation of the present study is the lack of neuroimaging or neuropathological confirmation of the VaD diagnosis. Although vascular factors clearly contributed to the dementia development in all VaD cases, it is likely that a certain amount of degenerative pathology was present in the incident VaD group, contributing to the cognitive deficits. Autopsy studies have found that brain changes in pathologically confirmed VaD and AD frequently overlap. Differential diagnosis, even with access to neuroimaging data, is rendered even more difficult in a sample of very old persons because mixed dementia is more common in this age group. However, the present findings are supported by the fact that other studies have observed preclinical MMSE impairment in VaD persons with neuroimaging confirmation of the diagnosis. In the present study, VaD diagnosis was restricted primarily to persons with poststroke dementia. Thus, the onset and progression of cognitive deficits may be different in other types of VaD (eg, small-vessel disease).

Both cognitive deficits and vascular problems are associated with an increased AD risk. This gives even more reason for being attentive to these signs among elderly people in general health care settings. Thus, lifestyle adjustments, such as changing dietary habits, and management of vascular risk factors, such as diabetes and hypertension, may help prevent both VaD and AD.

In summary, this study provides further evidence of a preclinical period with cognitive deficits in VaD. Along with previous observations, these results suggest that poor cognitive performance can be an indicator of both prodromal AD and prodromal VaD. Therefore, cognitive dysfunction in combination with vascular risk factors should be a strong indicator for using preventive measures against VaD.
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References
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