Is Mild Cognitive Impairment Prodromal for Vascular Dementia Like Alzheimer’s Disease?

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Background and Purpose—Individuals with mild cognitive impairment (MCI) are at increased risk of Alzheimer’s disease (AD) and probably other forms of dementia. Some subtypes of vascular dementia (VaD) may possess minor neuropathological changes of AD that may contribute to cognitive impairments. It was posited that MCI, identified by criteria described here, might present as a prodrome for VaD and AD.

Methods—Serial Mini-Mental State Examination was administered at 3- to 6-month intervals, and neuroimaging was performed annually. Subtle cognitive dysfunctions were weighted and measured according to MCI criteria defined here. Subjects identified with MCI were then followed up for an additional 3.88±3.01 years. Diagnoses of VaD and AD were made according to established criteria.

Results—During 3.72±2.94 years of follow-up of the original normative subjects, 73 of 291 (25.1%) developed MCI. Of the 27 subjects who developed VaD, 15 (55.6%) had prodromal MCI. Of these, two thirds were subclassified as having small-vessel dementia. The remaining 12 patients with VaD (44.4%) were diagnosed directly from a cognitively normal status without preceding MCI. These were predominantly multi-infarct or strategic-infarct dementia (66.7%). An additional 35 MCI subjects (47.9%) developed AD. Both VaD and AD diagnosed after MCI prodromes manifested similar spectral domains of cognitive impairments, which included memory, during their MCI stages.

Conclusions—In some VaD subtypes, particularly those caused by subcortical microvascular disease, dementia may be preceded by MCI, which has similar domains of cognitive impairment and a similar progressive course that may mimic AD. (Stroke. 2002;33:1981-1985.)

Key Words: Alzheimer disease ■ cognitive disorders ■ dementia, vascular ■ psychometrics ■ stroke

Alzheimer’s disease (AD) and vascular dementia (VaD) are the most prevalent dementias among the elderly. In the United States, AD is the most common; but in developing countries, cerebrovascular disease is the leading cause of dementia.1 Together, VaD and AD are responsible for 80% of all dementias.2,3 Traditionally, AD and VaD can be differentiated by separate risk factors, clinical course, neurological manifestations, and neuroimaging characteristics.4–6

In general, AD has insidious onset, followed by gradually progressive cognitive deterioration with little or no focal neurological symptoms and signs, and it has typical degenerative neuropathological features.7 It can be separated into predictable clinical stages ranging from prodromal mild cognitive impairment (MCI) to mild, moderate, and profound dementia.8,9 On the other hand, VaD is supposed to have an abrupt onset of dementia, followed by stepwise deterioration of cognitive performance associated with neurological signs and symptoms reflecting focal brain lesions.5,10 It has generally been accepted that cognitive functions deteriorate rapidly from normal at the time of or shortly after stroke, which warrants diagnosis of VaD.4,5 It has been assumed that there were no prodromal cognitive impairments, like MCI to AD, before onset of “stroke dementia.” This viewpoint obtained general support until about 1990, with multi-infarct dementia (MID) then being considered the main type of VaD.11

With widespread use of CT and MRI in the past decade, more complex interactions between different types of vascular lesions and cognitive impairments were defined. Likewise, more refined etiological and pathogenetic factors influencing VaD were identified.12–14 VaD has also been classified into at least 8 subtypes.15–18 Among these subtypes, MID and subcortical small-vessel dementia are the most common VaD.18 Subcortical small-vessel dementia incorporates a number of clinical entities: Binswanger’s disease, lacunar state, genetically determined cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), familial amyloid angiopathy, and coagulopathy.18–21 Unlike MID, subcortical dementia resulting from small-vessel disease has a relatively insidious onset with gradual cognitive deterioration.22,23 As a result, the following
question arises: Does an MCI stage precede some cases of VaD? This longitudinal study was designed to answer this question.

Subjects and Methods

Subjects
Subjects were volunteers enrolled in longitudinal studies of aging and dementia inaugurated in 1983 and approved annually by Institutional Review Boards at Baylor College of Medicine. These volunteers lived in Houston metropolitan or adjacent areas and were recruited from relatives and friends of outpatients with dementia or stroke. Many had a family history of AD or VaD, so the cohort was intentionally weighted to be at risk for dementia. Subjects with preexisting cognitive impairments or potentially fatal differences were excluded. Detailed criteria for inclusion and exclusion were reported elsewhere.24 A total of 291 (women, 46.4%; mean age, 67.86 ± 9.00) neurologically and cognitively normative subjects were impaneled and followed up longitudinally.

Subjects were scheduled for regular clinic visits at 3- to 6-month intervals. Mini-Mental State Examination (MMSE),25 Cognitive Capacity Screening Examination (CCSE),26 and Hamilton Depression Rating Scale27 were repeated at each visit. Ancillary evaluations included medical, neurological, and basal laboratory examinations. Cerebrospinal fluid analysis, electroencephalograms, ECGs, and xenon CT cerebral blood flow measurements were performed as indicated. Subjects underwent annual CT and MRI studies. All patients had at least 1 MRI scan on study admission. MRI studies were conducted at 1.5 T (Signa, General Electric Medical Systems) with T1- and T2-weighted flair imaging with coronal and sagittal sections. They were also followed up, as necessary, by monthly telephone interviews, and if subjects or caregivers expressed concern about possible deterioration in cognition or behavior, the subjects were asked to attend additional clinic visits for further evaluation. The purpose was to detect cognitive impairments or deterioration as early as possible to minimize interindividual partial differences.

Identification of MCI was made if subjects met the following criteria: (1) memory complaints, (2) normal activities of daily living, (3) absence of dementia, and (4) mild quantifiable impairments of cognitive function tested by MMSE, with cutoff points adjusted for age and education. Cutoff points were set at 1 SD below means for each population subgroup of given age and educational level.28 For example, for 70- to 74-year-old subjects with a college education, the cutoff point for MCI was 28–1.6 = 26.4, but for the same age-range group with only 5 to 8 years of education, the cutoff point was 26–1.8 = 24.2.

After MCI was identified, cognitive performance was tracked at 3- to 6-month intervals to determine whether cognitive deterioration reached different dementia criteria. After each visit, all assessment results (medical information, test performance, neuroimaging results, and clinical impressions) were reviewed. Diagnosis of AD was made according to NINCDS-ADRDA criteria4 and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.29 Diagnosis of VaD was made according to NINDS-AIREN criteria.5 The clinical features for VaD included sudden onset, stepwise progression, prolonged plateaus, periods of spontaneous improvement, and onset or worsening in relation to stroke or episode of hypoperfusion. Focal neurological signs or symptoms were strong supports of the diagnosis of VaD. Subjects in this study diagnosed as probable VaD all had abnormal neuroimaging. VaD subtype classifications were based on results of neuroimaging plus clinical evaluation.16,17,30 Patients having focal neurological symptoms or brain imaging suggestive of ischemia but with a gradual onset of or progressive decline in cognition were regarded as VaD and then subclassified according to their focal neurological lesions.

Neuropsychological Screening
MMSE was the principal psychometric instrument for screening cognitive functions. The more sensitive CCSE provided supplemental measurements. Because depression is common among the elderly and may confound cognitive evaluations,31,32 the Hamilton Depression Rating Scale was administered, together with MMSE and CCSE, to monitor any influences of depressive symptoms on cognitive performance.33 MMSE was administered according to standardized procedures, with a maximal score of 30. Subtests representing 5 different domains of cognition were analyzed: orientation, memory, attention and calculation, language, and design copying.25 Regarding attention and calculation subtests, in the work by Folstein et al.,24 subjects were asked to subtract serial 7s, and if a subject did not perform this task, he or she was asked to spell the word “world” backward. In the present study, all subjects were required to perform serial 7 substitutions to minimize interindividual difference because previous psychometric research indicates that these 2 items test different cognitive functions and exhibit discriminatory degrees of difficulty.34

Statistical Analysis
Unadjusted statistical analyses were performed with χ2 analysis for dichotomous results (Fisher’s exact test). Temporal conversion rates from MCI to dementia were compared by the Kaplan-Meier method. Longitudinal and intergroup comparisons were evaluated by independent t tests.

Results
During 3.72 ± 2.94 years of follow-up of normative subjects, 73 of 291 (25.1%) had met criteria for MCI and completed ≥1 MCI follow-up evaluations. The remaining 218 (74.9%) had retained cognitive functions above the MCI threshold at data analysis or at the time of dropout [25 (8.6%) died, 4 (1.4%) moved, and 13 (4.5%) declined to continue]. There were no significant differences among the outcome groups concerning dropout rates. Twenty-seven subjects developed VaD, of which 15 (55.6%) developed VaD from prodromal MCI and 12 (44.4%) developed VaD directly from normative cognitive status without prodromal MCI. The ratio for VaD developing from MCI (20.55%) was higher than the ratio for VaD developing from cognitively normal status (5.50%) during comparable follow-up (P<0.001). Among VaD with prodromal MCI, 10 of 15 (66.7%) were subclassified as subcortical small-vessel dementia, and 4 (26.7%) were classified as MID or strategic-infarct dementia. Among VaD without prodromal MCI, only 2 of 12 (16.7%) were subclassified as subcortical small-vessel dementia and 8 (66.7%) as MID or strategic-infarct dementia. As shown in Table 1, there were significant differences in subtype components between VaD developing from preceding MCI and VaD developing from a cognitively normal status (P<0.05).

| TABLE 1. Prevalence of Subtypes of VaD Developing From MCI and Cognitively Normal Status |
|-----------------|-----------------|-----------------|
|                  | VaD From MCI    | VaD From Cognitively Normal Status |
|                  | (n=15), n       | (n=12), n        |
| Subcortical small-vessel dementia | 10               | 2*               |
| MID or strategic-infarct dementias | 4               | 8*               |
| Hemorrhagic dementia | 1               | 1*               |
| Combined cortical and subcortical dementia | 0               | 1*               |

*There is a significant difference (P<0.05) between all subtype constituents of VaD developing from MCI and VaD developing from cognitively normal status by χ2 test.
During 3.88±3.01 years of MCI follow-up, 35 (47.9%) developed AD, 15 (20.5%) developed VaD, and the remaining 23 (31.5%) exhibited persistent MCI or showed improvement at the time of data analysis. Table 2 displays demographic factors at the time MCI was identified according to outcomes. Those developing AD had fewer years of education than those with persistent MCI (P<0.05). No significant differences were detected regarding age, sex, vascular risk factors, or family history of neurodegenerative diseases for those later developing AD, VaD, or persistent MCI.

Figure 1 displays 5 subtest scores for MMSE comparing 3 MCI outcome groups at the time MCI was identified. All 3 groups showed relatively low scores for memory subtest and relatively high scores for language and orientation subtests. MCI subjects who later developed AD, however, got lower scores for attention subtests compared with persistent MCI subjects at the time MCI was identified (P<0.05). Memory subtest scores decreased similarly in 3 MCI outcome groups and did not predict AD.

As shown in Figure 2, before diagnosis of dementia, there were no significant differences for MMSE total and 5 subtest scores comparing those developing AD and those developing VaD (Figure 2). After dementia was diagnosed, cognitive test performance for VaD versus AD evolved quite differently, with AD showing continuous and relatively rapid deterioration while VaD stabilized or even improved as follow-up continued. Twenty-four months after diagnosis of dementia, MMSE total scores for AD were lower than for VaD (P<0.05).

**Discussion**

VaD has a more heterogeneous origin, pathogenesis, and clinical course compared with AD. According to different tempos of dementia onset, VaD can be separated into 2 groups. One has abrupt onset caused predominantly by multi-infarct, strategic-infarct, or intracranial hemorrhage; the other has insidious onset, caused predominantly by subcortical small-vessel disease. Although there is some overlap and no clearcut line can be drawn between the 2 groups, efforts to distinguish them according to dementia onset have clinical merit. Early identification of insidious-onset VaD, which may have prodromal manifestations like MCI, whether alone or mixed with AD, introduces an opportunity for clinical interventions such as control of vascular risk factors that may minimize, arrest, or even reverse cognitive deterioration.

Subcortical small-vessel disease is an important cause of VaD of insidious onset. The proportion of VaD attributable to subcortical small-vessel disease ranges from 36% to 67% according to different authors and is higher among nonwhites. Unlike typical MID, particularly that caused by large cortical infarcts, VaD caused by subcortical small-vessel disease has a relatively insidious onset due to gradually progressive microvascular changes identifiable by neuroimaging methods producing a clinical course mimicking AD. Hypertensive arteriolar lipohyalinosis involving...
small penetrating vessels (cerebral microangiopathy) is responsible for most lacunar infarctions and deep white-matter lesions causing VaD. These neuropathological changes associated with hypertension, hyperlipidemia, diabetes mellitus, or genetically related cerebrovascular diseases (eg, CADASIL) are present a relatively long time before VaD becomes diagnosable and can be expected to cause subtle cognitive impairments. Some subtypes of VaD also have minor neuropathological elements of AD, which synergistically contribute to cognitive decline. According to the present longitudinal study, most (83.3%) subcortical small-vessel dementias exhibit prodromal MCI (Table 1).

From analysis of 5 subtest scores of MMSE, the present study failed to find differences between VaD and AD in their predementia spectra of cognitive impairments (Figure 1) or in their predementia course of progression (Figure 2). But after dementia was diagnosed, their courses of cognitive impairment and prognoses were quite different. Hachinski and Erkinjuntti and Rockwood suggested the term “vascular cognitive impairment” to include all cognitive impairments of cerebrovascular origin. The importance of early identification of vascular cognitive impairment was also emphasized, and the term “vascular cognitive impairment no dementia” was suggested to depict subtle cognitive impairments that did not meet VaD criteria. Recently, Petersen et al hypothesized that multiple-domain MCI is likely progress to VaD, where single-domain amnestic MCI is likely progress to AD. Because it is currently impossible to predict which types of prodromal cognitive impairment will progress to VaD, progress to AD, or keep the status quo, or even improve, MCI seems the most suitable term for depicting predementia cognitive impairments.

As a clinical entity aimed at the prevention of dementia before it becomes established, MCI criteria must be strict, valid, and reliable. But criteria of MCI meeting these requirements are far from well established. In criteria suggested by Petersen et al, memory impairment was considered the only component of MCI. Bozoki et al showed that memory loss alone rarely progresses to dementia in the subsequent 2 years. However, the risk of dementia is significantly increased among patients with clear domains of cognitive impairments beyond memory loss. These results indicate that differences in the identification of MCI will influence dementia outcome.

An admitted limitation of this study is the use of MMSE for both MCI identification and follow-up. Although MMSE is frequently used to evaluate cognitive impairments, it has shortcomings, one of which is its insensitivity in detecting subtle cognitive impairments, particularly among the highly educated, CCSE, a more sensitive instrument, was used in this study to complement MMSE. The specificity of subtests for measuring impaired domains of cognition during MCI staging requires further investigation.

Conclusions
Some VaD subtypes, particularly those caused by subcortical small-vessel disease, are preceded by MCI with progression mimicking AD. After diagnosis of dementia, AD and VaD follow different cognitive courses.

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References
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