Intracranial artery stenosis and progression from mild cognitive impairment to Alzheimer disease

Jie Zhu, MD
Yanjiang Wang, MD, PhD
Jing Li, MD, PhD
Juan Deng, MD, PhD
Huadong Zhou, MD, PhD

Correspondence to Dr. Zhou: neuro_hdzhou@yahoo.com

ABSTRACT

Objective: To assess the impact of intracranial arterial stenosis on the progression from mild cognitive impairment (MCI) to Alzheimer disease (AD).

Methods: A total of 423 participants with MCI were included and evaluated with clinical and neuropsychological examinations annually for 4 years. The incidence of dementia due to AD was investigated. CT angiography was used to measure the stenosis of major intracranial arteries in the studied population. A mixed-effects regression model was used to analyze the association between intracranial arterial stenosis and the progression of MCI, which was assessed with the Mini-Mental State Examination and the Activities of Daily Living scale. Cox proportional hazards models were used to identify the association between intracranial arterial stenosis and dementia progression.

Results: At the end of the follow-up, 116 participants had progressed to dementia due to AD, while 223 remained in the MCI stage. Participants with moderate or severe intracranial arterial stenosis had a faster decline in cognition and function relative to participants without such stenosis. The presence of moderate or severe intracranial arterial stenosis significantly increased the risk of dementia progression, even after controlling for age, sex, education, vascular risk factors, and silent MRI lesions.

Conclusions: Intracranial arterial stenosis increased the risk of developing AD dementia after MCI. *Neurology*® 2014;82:842–849

GLOSSARY

AD = Alzheimer disease; **ADL** = Activities of Daily Living; **CTA** = CT angiography; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **HIS** = Hachinski Ischemic Score; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **VaD** = vascular dementia; **VRF** = vascular risk factor; **WMH** = white matter hyperintensity.

Alzheimer disease (AD) is the most common age-related dementia and has become a severe public health problem affecting the increasing senior population.[1] Therapeutic strategies for AD should be based in part on the prevention of disease progression by initiating treatment as early as possible. Mild cognitive impairment (MCI) is a transitional stage between normal cognitive function and dementia.[2] Improved ability to predict risk of imminent decline in patients with MCI is important for individual patient risk stratification as aggressive new treatments are developed.

Current results from a large number of studies suggest that during the pathogenesis and development of the majority of AD cases, degenerative and vascular lesions coexist and interact, thereby exacerbating cognitive damage.[3–6] An inefficient blood supply to the brain has very grave consequences on brain function. Thus, in addition to age-related hemorheologic decline, vascular disease probably affects AD pathogenesis and development in some patients. In a series of autopsy studies, Roher et al. found that the incidence and severity of intracranial atherosclerotic stenosis in the circle of Willis were significantly greater in individuals with AD than in individuals without dementia.[7–9] However, few studies have focused on the relationship between intracranial atherosclerotic stenosis and the progression from MCI to AD dementia.

From the Department of Neurology, Daping Hospital, Third Military Medical University, Chongqing, China.
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

In the present prospective study, we used the CT angiography (CTA) method to perform follow-up evaluations of stenosis in major intracranial arteries in the studied population in order to determine whether intracranial arterial stenosis increased the risk of progression from MCI to AD dementia.

METHODS

Study subjects. We consecutively recruited 423 participants with MCI from the inpatients in the Department of Neurology of Daping Hospital in the city of Chongqing, from December 1, 2006 through November 30, 2007. The eligibility requirements included participants in the following categories: (1) 55 years of age and older, and (2) long-term residents of these communities. The exclusion criteria were (1) a diagnosis of dementia, (2) a concomitant neurologic disorder potentially affecting cognitive function (e.g., severe Parkinson disease), (3) a history of stroke, (4) a stenosis of 20% or more in the extracranial internal carotid artery and vertebral artery, (5) the inability to comply with the study assessment, (6) enduring mental illness, (7) drug abuse, and (8) moving away or declining to participate.

Standard protocol approvals, registrations, and patient consents. This study was approved by the Institutional Review Board of the Third Military Medical University, and all of the participants and their caregivers provided written informed consent.

Determination of intracranial arterial stenosis. CTA was performed using a 64-slice CT scanner (Light Speed VCT 64-slice Scanner; General Electric, Milwaukee, WI). Two readers who were blinded to the participants' clinical information independently reviewed all CTA images for the presence and degree of stenosis. The assessment included the intracranial internal carotid arteries; the anterior, middle, and posterior cerebral arteries (proximal segments such as A1, M1, and P1, as well as distal segments or the communicating arteries, if present); and the vertebrobasilar arteries (basilar and bilateral intracranial vertebral). The degree of stenosis was calculated using the method published for the Warfarin-Aspirin Symptomatic Intracranial Disease Study: percent stenosis = $[(1 - (D_{stenosis}/D_{normal})] \times 100$.[10] If one artery had multiple stenotic lesions, the most severe degree was selected.

The degree of stenosis was divided into 3 grades, according to the methods of Dolan et al.[11] Grade 1 intracranial arterial stenosis (n = 133) required stenosis of less than 20% in any vessel. Grade 3 (n = 86) required stenosis of 40% or greater in 2 or more vessels. Grade 2 (n = 204) was assigned to intermediate lesions, which predominantly included single-vessel disease or multiple low-grade stenoses. Intra- and interobserver reproducibility was determined to be 0.91 and 0.86, respectively.

Neuropsychological assessment. Cognitive and functional status was assessed using the Chinese version of the Mini-Mental State Examination (MMSE) and the Activities of Daily Living (ADL) scale, which were previously validated in Chinese elderly individuals.[12] The patients with cognitive decline upon MMSE screening were further administered a battery of neuropsychological tests that was developed for epidemiologic dementia studies on all types of subjects.[12] This neuropsychological battery included the following assessments: the Fuld Object Memory Evaluation, for detecting extensive cognitive dysfunction mainly composed of memory[13]; a test of Rapid Verbal Retrieval, for assessing semantic memory[14]; the Wechsler Adult Intelligence Scale, for evaluating immediate memory and graphical recognition[15]; the Pfeiffer Outpatient Disability Questionnaire, for assessing the ability to engage in social activities[16]; the Hamilton Depression Rating Scale, for measuring emotional status[17]; and the Hachinski Ischemic Score (HIS) for evaluating significant vascular disease.[18]

Diagnosis of MCI. The operational definition of MCI was based on clinical judgment and patient history, according to the established Mayo Clinic criteria.[2] These criteria included (1) subjective complaints of memory deficits, (2) abnormal memory functioning for age, (3) the absence of dementia based on the diagnostic examination (Clinical Dementia Rating ≤ 0.5), and (4) normal everyday functioning upon ADL assessment. The participants with depressive disorders were excluded.[19]

Diagnosis of AD. AD was clinically diagnosed by a group of senior neurologists and psychiatrists, who followed the protocol described in our previous studies.[12] In brief, dementia was diagnosed based on criteria modified from the *DSM-IV*.[20] We made a diagnosis of AD based on the criteria of the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association.[21] The diagnosis of vascular dementia (VaD) was based on the criteria of the National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences.[22] The differentiation of AD from VaD is based on the National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria and HIS (HIS ≤ 4: AD; $4 <$ HIS < 7: mixed dementia; HIS ≥ 7: VaD).[19,21] The endpoint in the time-to-event analysis was the diagnosis of dementia.

Clinical assessment. The demographic data collected consists of age, sex, and education level (a lower education level refers to ≤ 6 years of schooling, whereas a higher education level refers to > 6 years of schooling).

The vascular risk factors (VRFs) were determined from a structured clinical interview (with the caregivers' involvement) and the physical and laboratory examinations as previously described.[23,24] The risk factors included in our analyses were hypertension, diabetes, hypercholesterolemia, TIA, atrial fibrillation, and a history of myocardial infarction, smoking, and alcohol use. Fasting blood samples were collected for measuring the fasting levels of glucose, total cholesterol, low-density lipoprotein, lipoprotein(a), and homocysteine, as well as *APOE* genotype.

MRI analysis. We performed a multisequence MRI protocol on a 3.0-tesla scanner (MAGNETOM Verio 3.0T; Siemens, Erlangen, Germany). The sequences in the imaging protocol consisted of 3 high-resolution axial scans, i.e., a T1-weighted sequence, a T2-weighted sequence, and a fluid-attenuated inversion recovery sequence. All of the MRI scans were reviewed by 2 trained raters (Li et al.) who were blinded to the clinical data.

White matter hyperintensity (WMH) was scored using the visual scale developed by Fazekas et al.[25] The lesions were classified into 3 categories and graded as follows: absent = 0; mild = 1 (single lesions smaller than 10 mm or areas of grouped lesions smaller than 20 mm in any diameter); moderate = 2 (single lesions between 10 and 20 mm, areas of grouped lesions more than 20 mm in any diameter, or no more than connecting bridges between individual lesions); and severe = 3 (single lesions or confluent areas of hyperintensity 20 mm or more in any diameter).

The lacunar infarcts were recorded according to their number. Lacunar infarcts were defined as cavities with a diameter of 3 to 10 mm and signal intensities similar to the CSF in all scan sequences, using a combination of fluid-attenuated inversion recovery and T2 images to distinguish the lacunar infarcts from Virchow-Robin spaces and microbleeds.[26]

Follow-up. In total, 423 patients who were enrolled in the present study participated in follow-up assessments for 4 years, from December 2007 to December 2011. Demographic data and VRFs were collected at the baseline visit. The same neuropsychological tests were administered annually by a neuropsychologist who was blinded to the medical records of the participants. All of the participants were examined by CTA and MRI, both at entry and at the final follow-up visit.

Statistical analysis. In the univariate analyses, baseline variables were analyzed using *t* tests when data were independent, normally distributed, and continuous; χ^2 tests when data were categorical; and Mann-Whitney *U* tests for ordinal and categorical variables that were not normally distributed.

Mixed-effects regression models were used to identify the effects of time and intracranial arterial stenosis on cognitive and functional decline, defined as MMSE and ADL changes between the baseline and follow-up visits. The assessment year (baseline, first, second, third, and fourth follow-up year) served as a within-subject variable. The MMSE and ADL scores were set as dependent variables separately. The grades of intracranial arterial stenosis were set as predictor variables. We performed mixed-model analyses with an unstructured covariance structure. For each dependent variable, the interaction terms with time represent the effects of the variables on the rate of change in cognitive score.

The association between the grade of intracranial arterial stenosis and incident dementia due to AD was calculated using Cox proportional hazards regression models in 2 steps. Intracranial arterial stenosis was included in the Cox model to assess the association between this variable and incident dementia due to AD. Next, all of the analyses were adjusted for age, sex, and level of education. Additional adjustments were made for VRFs (i.e., hypertension, diabetes, TIA, current smoking, and *APOE* genotype). Further analyses also adjusted for the presence of WMH and lacunar infarcts.

RESULTS

In total, 423 participants with MCI were enrolled in the study at baseline. Of these, 339 participants (80.1%) completed the follow-up, 19 (4.5%) withdrew, and 65 (15.4%) developed VaD (including 21 with mixed dementia) and were excluded from the current analyses. Among the participants who withdrew, 8 died and 11 declined. Ultimately, 116 (27.4%) developed dementia due to AD, and 223 (52.7%) remained in the MCI stage. No other types of dementia were detected in the present study. The progression rate from MCI to dementia due to AD was 6.9% per year.

Baseline characteristics. The demographic, clinical, and MRI characteristics of the participants who remained in the MCI stage or progressed to dementia due to AD are summarized in table 1. Compared with the participants who remained in the MCI stage, those who progressed were older, more likely to be female, had lower education levels, and displayed a higher frequency of hypertension, diabetes, TIA, current smoking, and *APOE*. The severity of WMH and intracranial artery stenosis was higher in the patients who progressed to dementia due to AD compared with those who did not progress.

Association between intracranial artery stenosis and the progression of MCI. Results of the mixed-effects regression analysis for intracranial arterial stenosis are presented in table 2. Participants with grades 2 and 3 intracranial arterial stenosis declined more rapidly on the MMSE, with an annual decline of 0.40 and 1.21, respectively, compared with 0.22 for participants with grade 1 intracranial arterial stenosis (figure 1A). Results were similar for ADL score. Compared with participants with grade 1 intracranial arterial stenosis, participants with grades 2 and 3 intracranial arterial stenosis showed a faster rate of function decline (figure 1B). There were no differences between participants with grades 2 and 3 intracranial arterial stenosis in decline in both of the cognitive scores.

Association between intracranial artery stenosis and AD progression. Table 3 and figure 2 show the Cox regression analysis for the association between intracranial arterial stenosis and incident dementia due to AD. Compared with the participants with grade 1 intracranial arterial stenosis, participants with grade 2 intracranial arterial stenosis had a hazard ratio of 2.6, and participants with grade 3 intracranial artery stenosis had a hazard ratio of 2.9. The association remained statistically significant after adjusting for age, sex, and education (model 1 in table 3). The magnitude of the effect was not changed by additional adjustment for VRFs (model 2 in table 3). The results remained statistically significant when examining the association between grade 2 or grade 3 intracranial arterial stenosis and a higher risk of incident dementia due to AD when correcting for cerebral WMH and lacunar infarcts (model 3 in table 3).

DISCUSSION

The role of atherosclerosis in the pathogenesis and development of AD is controversial, and the relationship between dementia and atherosclerosis without clinical signs of stroke remains unclear.[27,28] Findings from a series of autopsy studies have shown that the incidence and severity of intracranial atherosclerotic stenosis in the circle of Willis are significantly greater in patients with AD than in elderly individuals without AD.[7–9,29,30] Autopsy studies have also suggested that intracranial arterial stenosis may either be involved in the AD pathologic pathway[7–9,29,30] or have an independent, synergistic role.[11,31] Two studies have used transcranial Doppler to investigate the relationship between atherosclerosis in the circle of Willis and the diagnosis of AD

Table 1 Baseline characteristics of the participants with MCI who remained in the MCI stage or progressed to AD dementia

Characteristics	Stayed in MCI (n = 223)	Progressed to AD (n = 116)	p
Demographics			
Age, y, mean ±SD	63.3 ± 6.8	65.9 ± 8.6	0.003
Female, n (%)	107 (48.0)	69 (59.4)	0.044
Lower educational level (≤6 y), n (%)	70 (31.4)	54 (46.6)	0.006
Cognition assessment			
MMSE, mean ± SD	26.3 ± 2.4	26.1 ± 1.9	0.433
ADL, mean ± SD	26.2 ± 3.9	26.8 ± 4.5	0.166
Vascular risk factors			
Hypertension, n (%)	62 (27.8)	46 (39.7)	0.026
Diabetes, n (%)	40 (17.9)	33 (28.4)	0.026
Hypercholesterolemia, n (%)	58 (26.0)	38 (32.8)	0.191
Myocardial infarction, n (%)	9 (4.0)	5 (4.3)	0.904
Atrial fibrillation, n (%)	16 (7.2)	12 (10.3)	0.314
TIA, n (%)	39 (17.5)	32 (27.6)	0.030
Daily alcohol use, n (%)	20 (9.0)	17 (14.7)	0.111
Current smoking, n (%)	24 (10.8)	22 (18.9)	0.036
Laboratory examination			
APOE, n (%)	51 (22.9)	39 (33.6)	0.033
Lipoprotein(a), mg/L, mean ± SD	188.7 ± 35.9	196.1 ± 37.4	0.071
Homocysteine, μmol/L, mean ± SD	13.8 ± 7.3	15.6 ± 6.3	0.129
MRI findings			
WMH (Fazekas scores), mean ± SD	2.0 ± 1.3	2.6 ± 1.2	0.010
Lacunar infarcts, n (%)	85 (43.9)	45 (46.7)	0.903
Intracranial artery stenosis, moderate or severe (grades 2 and 3), n (%)	139 (62.3)	98 (84.5)	<0.001

Abbreviations: AD = Alzheimer disease; ADL = Activities of Daily Living; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; WMH = white matter hyperintensities.

in vivo.[32,33] These investigations revealed that, compared with elderly individuals who had normal cognitive function or patients with MCI, the patients with AD exhibited significantly greater pulsatility indices for the examined arterial segments and significantly lower mean flow velocities of these segments. The increased pulsatility indices and decreased mean flow velocities were closely associated with the clinical

Table 2 Mixed-effects regression model measuring the association between intracranial arterial stenosis severity and the decline in cognition and function in patients with MCI[a]

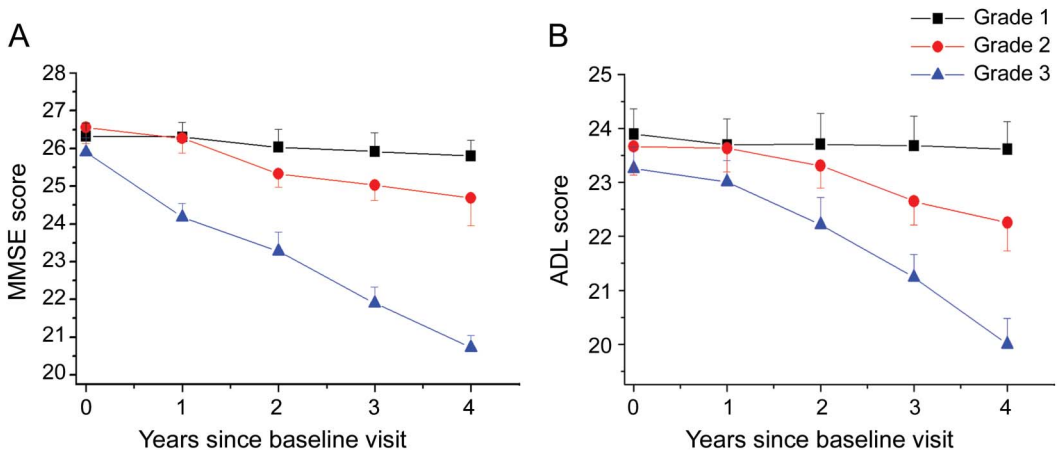
		Cognition (MMSE)		Function (ADL)	
Variable	N (%)	β (SE)	p[b]	β (SE)	p[b]
Grade 1	102 (30.1)	−0.22 (0.05)		−0.18 (0.03)	
Grade 2	165 (48.7)	−0.40 (0.08)	<0.001	−0.39 (0.08)	<0.001
Grade 3	72 (21.2)	−1.21 (0.13)	<0.001	−1.11 (0.18)	<0.001

Abbreviations: ADL = Activities of Daily Living; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; SE = standard error.

[a] Mixed-effects regression model was used to estimate rates of decline in MMSE and ADL scores over time. Intracranial arterial stenosis severity was entered as categories to obtain estimated annual change for every grade and to compare rates of decline between individuals with grade 2 or 3 intracranial arterial stenosis vs those with grade 1 intracranial arterial stenosis. β represents the difference in annual rate of change on the MMSE or ADL.

[b] The *p* value for comparison to grade 1 intracranial arterial stenosis.

Figure 1 Relationship between intracranial arterial stenosis severity and the rate of cognitive decline



Data shown are the mean predicted MMSE and ADL scores with standard error based on output from a mixed-effects regression model. Significant interaction between intracranial arterial stenosis severity and time for the decline in MMSE score (A) and ADL score (B). Higher annual rate of cognitive decline was associated with higher grade of intracranial arterial stenosis. ADL = Activities of Daily Living; MMSE = Mini-Mental State Examination.

diagnosis of AD. We hypothesize that intracranial arterial stenosis might promote the progression from MCI to dementia in patients with underlying AD pathology.

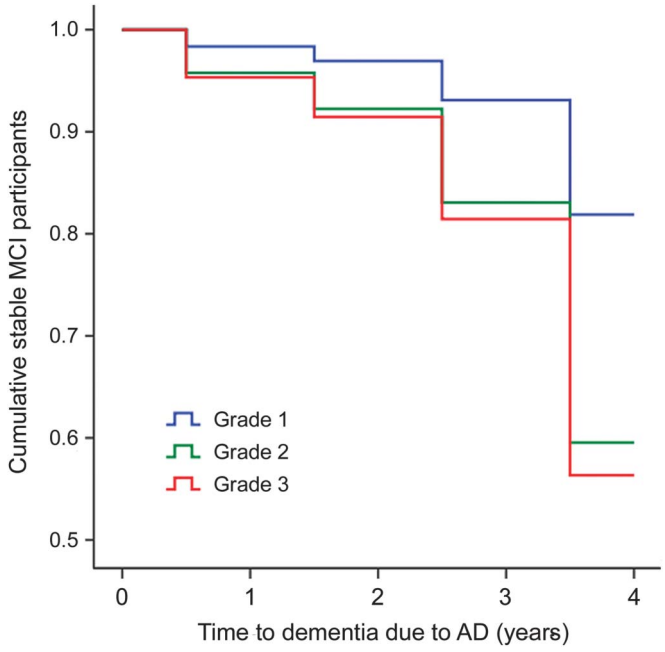
Epidemiologic studies suggest that risk factors related to atherosclerotic vascular disease (such as hypertension, dyslipidemia, diabetes, obesity, and smoking) can increase the risk of MCI and AD.[23,34–37] In our previous study,[23] we found that VRFs in either composite or individual measures were associated with the higher risk of progression from MCI to AD, while treatment of VRFs can delay progression in subjects with MCI. Prior work from our research group[37] also found that diabetes, severity of white matter changes, moderate to severe carotid stenosis, and carotid stenosis change during follow-up were predictors of progression from MCI to AD. The current study provided evidence that intracranial arterial stenosis increases the risk of developing AD after MCI. To our knowledge, the present study is one of the foremost prospective cohort studies using research participants from a Chinese population to observe the correlations between intracranial arterial stenosis and AD risk. Another strength of our study is that we used CTA to perform follow-up evaluations of stenosis in major intracranial arteries in the studied population. Although transcranial Doppler is widely used for examining cerebrovascular disease because of its ease of use and low cost, this scanning technique cannot visualize blood vessels. CTA is an examination method that is frequently used in clinical practice; this approach can independently and accurately assess intracranial arterial stenosis. Compared with digital subtraction angiography, which is the gold standard in the field, the sensitivity and specificity of CTA for the diagnosis of intracranial arterial stenosis/occlusion may reach 97.1% and 99.5%, respectively.[38] However, CTA is a noninvasive examination method and is less expensive and more widely available than digital subtraction angiography. CTA is also superior to

Table 3 Association between intracranial arterial stenosis severity and progression from MCI to AD dementia, as assessed by the Cox proportional hazards regression model

			Adjusted HR for AD (95% CI)[a]					
	Crude HR for AD (95% CI)	*p*	Model 1	p^{a1}	Model 2	p^{a2}	Model 3	p^{a3}
Grade 2 vs grade 1	2.6 (1.5–4.4)	<0.001	2.4 (1.4–4.0)	0.001	1.9 (1.1–3.3)	0.026	1.9 (1.1–3.3)	0.028
Grade 3 vs grade 1	2.9 (1.6–5.2)	<0.001	2.7 (1.5–4.8)	0.001	2.0 (1.0–3.9)	0.039	2.0 (1.0–3.8)	0.043
Grade 3 vs grade 2	1.1 (0.7–1.7)	0.672	1.1 (0.7–1.7)	0.633	1.0 (0.6–1.6)	0.957	1.0 (0.6–1.5)	0.873

Abbreviations: AD = Alzheimer disease; CI = confidence interval; HR = hazard ratio; MCI = mild cognitive impairment.
[a] Model 1: adjusted for age, sex, and level of education. Model 2: additionally adjusted for vascular risk factors (i.e., hypertension, diabetes, TIA, current smoking, and *APOE*). Model 3: additionally adjusted for MRI lesions (cerebral white matter hyperintensities and lacunar infarcts). The *p* value of adjusted HR of the progression from MCI to AD dementia compared with the participants with grade 1 intracranial arterial stenosis.

Figure 2 Incidence of progression to AD



Kaplan-Meier curves for AD progression among subjects with MCI grouped according to intracranial arterial stenosis severity. Green and red lines indicate participants with grades 2 and 3 intracranial arterial stenosis, respectively. The blue line indicates participants with grade 1 intracranial arterial stenosis. The *p* value is 0.028 comparing participants with grade 2 to those with grade 1 intracranial arterial stenosis and 0.043 comparing participants with grade 3 to those with grade 1 intracranial arterial stenosis. AD = Alzheimer disease; MCI = mild cognitive impairment.

other vascular imaging techniques for observing changes in and the calcification of intracranial arterial walls.[39]

In our study, we adjusted analyses for a series of possible confounding factors (including demographics, VRFs, WMH, and lacunar infarction) that are associated with an increased risk of AD.[23,35,36,40] This adjustment did not influence the association between intracranial arterial stenosis and the risk of MCI progression. This suggests that intracranial atherosclerosis might have some independent effects on the progression from MCI to AD dementia. First, atherosclerosis not only produces vascular distortions and entanglement but also causes mechanical obstruction of the major intracranial blood vessels. Moreover, atherosclerotic stenosis of large intracranial blood vessels may indicate systemic atherosclerosis, and widespread microvascular lesions cause microcirculation defects, increased resistance in small blood vessels, and reduced vascular reactivity, resulting in decreased cerebral perfusion. The cumulative effects of these interdependent hemodynamic dysfunctions may have a pivotal role in accelerating the pathogenesis and progression of AD.

Limitations to our analyses should be noted. First, because of its simplicity and reliability, the MMSE is widely used to assess cognitive dysfunction, and the validity of the MMSE for assessments of elderly Chinese populations has been widely recognized.[12] However, although the MMSE exhibits high sensitivity for attention, memory, and language, the test does not address all areas of cognitive function; in particular, the MMSE is severely limited in the evaluation of deficits in executive function. Therefore, we combined the MMSE with the ADL assessment, which reflects the participants' executive dysfunction. However, in future studies, more extensive tests would be helpful to detect the changes in different cognitive domains and observe the correlations between intracranial arterial stenosis in different locations with decreases in the various aspects of cognitive function. Moreover, although our study is prospective, our participants are not generalizable to people with MCI not admitted to hospital, which could have biased the results. Finally, we excluded participants with a degree of extracranial internal carotid artery and vertebral artery stenosis greater than 20%. The data on them would have added strength to this study.

The results of the present study suggest that patients with MCI who have intracranial arterial stenosis are more likely to experience deterioration in cognitive function and to progress to dementia due to AD. Currently, given the inability to identify specific and effective treatment methods for AD, assessments of the extent of intracranial arterial stenosis may be used as an effective clinical tool to predict patients' risk of developing AD. Moreover, by implementing lifestyle improvements and administering antiatherosclerosis drugs, it may be possible to prevent the occurrence of AD or to delay AD progression in these patients.

AUTHOR CONTRIBUTIONS

Dr. J. Zhu conducted the statistical analyses, interpreted the data, and drafted the original manuscript. Dr. Y. Wang conceptualized the study, reviewed the analyses, and proofread the manuscript. Dr. J. Li performed MRI assessment. Dr. J. Deng performed data acquisition. Dr. H. Zhou researched the literature and designed the study.

ACKNOWLEDGMENT

The authors thank Dr. Jiachuan Yan and Dr. Lin Wang for their instruction in performing this study.

STUDY FUNDING

Supported by the Chongqing Science and Technology Commission (2008AB0011) and National Nature Science Foundation of China (81000507).

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received June 3, 2013. Accepted in final form November 22, 2013.

REFERENCES

1. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005;366:2112–2117.

2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
3. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease: the Nun Study. JAMA 1997;277:813–817.
4. Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. Neurology 2004;62:1148–1155.
5. Spilt A, Weverling-Rijnsburger AW, Middelkoop HA, et al. Late-onset dementia: structural brain damage and total cerebral blood flow. Radiology 2005;236:990–995.
6. Johnson NA, Jahng GH, Weiner MW, et al. Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. Radiology 2005;234:851–859.
7. Roher AE, Esh C, Kokjohn TA, et al. Circle of Willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. Arterioscler Thromb Vasc Biol 2003;23:2055–2062.
8. Roher AE, Esh C, Rahman A, Kokjohn TA, Beach TG. Atherosclerosis of cerebral arteries in Alzheimer disease. Stroke 2004;35(11 suppl 1):2623–2627.
9. Beach TG, Wilson JR, Sue LI, et al. Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta Neuropathol 2007;113:13–21.
10. Samuels OB, Joseph GJ, Lynn MJ, Smith HA, Chimowitz MI. A standardized method for measuring intracranial arterial stenosis. AJNR Am J Neuroradiol 2000;21:643–646.
11. Dolan H, Crain B, Troncoso J, Resnick SM, Zonderman AB, Obrien RJ. Atherosclerosis, dementia, and Alzheimer disease in the Baltimore Longitudinal Study of Aging cohort. Ann Neurol 2010;68:231–240.
12. Zhou DH, Wang JY, Li J, Deng J, Gao C, Chen M. Study on frequency and predictors of dementia after ischemic stroke: the Chongqing stroke study. J Neurol 2004;251:421–427.
13. Fuld PA. The Fuld Object-Memory Evaluation. Chicago: Stoelting Instrument Co.; 1981:1–99.
14. Zhang M. Prevalence study on dementia and Alzheimer disease [in Chinese]. Zhonghua Yi Xue Za Zhi 1990;70:424–428, 430.
15. Welsh KA, Butters N, Hughes JP, Mohs RC, Heyman A. Detection and staging of dementia in Alzheimer's disease: use of the neuropsychological measures developed for the Consortium to Establish a Registry for Alzheimer's Disease. Arch Neurol 1992;49:448–452.
16. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. J Am Geriatr Soc 1975;23:433–441.
17. Kørner A, Lauritzen L, Abelskov K, et al. The Geriatric Depression Scale and the Cornell Scale for Depression in Dementia: a validity study. Nord J Psychiatry 2006;60:360–364.
18. Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke–Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006;37:2220–2241.
19. Palmer K, Di Iulio F, Varsi AE, et al. Neuropsychiatric predictors of progression from amnestic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. J Alzheimers Dis 2010;20:175–183.
20. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. Washington, DC: American Psychiatric Association; 1994.
21. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
22. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–260.
23. Li J, Wang YJ, Zhang M, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. Neurology 2011;76:1485–1491.
24. Zhou H, Deng J, Li J, Wang Y, Zhang M, He H. Study of the relationship between cigarette smoking, alcohol drinking and cognitive impairment among elderly people in China. Age Ageing 2003;32:205–210.
25. Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJNR Am J Neuroradiol 1987;8:421–426.
26. Gouw AA, van der Flier WM, Fazekas F, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the leukoaraiosis and disability study. Stroke 2008;39:1414–1420.
27. Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet 2004;363:1139–1146.
28. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197–2204.
29. Yarchoan M, Xie SX, Kling MA, et al. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. Brain 2012;135(pt 12):3749–3756.
30. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. Neurology 2005;64:494–500.
31. Luoto TM, Haikonen S, Haapasalo H, et al. Large vessel cerebral atherosclerosis is not in direct association with neuropathological lesions of Alzheimer's disease. Eur Neurol 2009;62:93–98.
32. Roher AE, Garami Z, Alexandrov AV, et al. Interaction of cardiovascular disease and neurodegeneration: transcranial Doppler ultrasonography and Alzheimer's disease. Neurol Res 2006;28:672–678.
33. Roher AE, Garami Z, Tyas SL, et al. Transcranial Doppler ultrasound blood flow velocity and pulsatility index as systemic indicators for Alzheimer's disease. Alzheimers Dement 2011;7:445–455.
34. Hofman A, Ott A, Breteler MM, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet 1997;349:151–154.
35. McIlroy SP, Dynan KB, Lawson JT, Patterson CC, Passmore AP. Moderately elevated plasma homocysteine, methylenetetrahydrofolate reductase genotype, and risk for stroke, vascular dementia, and Alzheimer disease in Northern Ireland. Stroke 2002;33:2351–2356.

36. Ott A, Slooter AJ, Hofman A, et al. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. Lancet 1998;351:1840–1843.
37. Li L, Wang Y, Yan J, et al. Clinical predictors of cognitive decline in patients with mild cognitive impairment: the Chongqing aging study. J Neurol 2012;259:1303–1311.
38. Nguyen-Huynh MN, Wintermark M, English J, et al. How accurate is CT angiography in evaluating intracranial atherosclerotic disease? Stroke 2008;39:1184–1188.
39. Homburg PJ, Plas GJ, Rozie S, van der Lugt A, Dippel DW. Prevalence and calcification of intracranial arterial stenotic lesions as assessed with multidetector computed tomography angiography. Stroke 2011;42:1244–1250.
40. Prins ND, van Dijk EJ, den Heijer T, et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. Brain 2005;128(pt 9):2034–2041.

Intracranial artery stenosis and progression from mild cognitive impairment to Alzheimer disease

Jie Zhu, Yanjiang Wang, Jing Li, et al.

Neurology 2014;82;842-849 Published Online before print January 31, 2014
DOI 10.1212/WNL.0000000000000185