Cognitive Correlates of Cerebral Vasoreactivity on Transcranial Doppler in Older Adults

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Background: This study was performed to explore the possible contributions of cerebral hemodynamic changes to the cognitive impairment in patients with Alzheimer's disease (AD). *Methods:* A total of 194 participants were included: 52 controls, 75 patients with mild cognitive impairment (MCI), and 67 patients with AD. Demographic characteristics, vascular risks, mini-mental state examination (MMSE), and clinical dementia rating (CDR) were assessed, and magnetic resonance imaging of the brain was performed to evaluate white matter hyperintensities (WMHs). Using transcranial Doppler (TCD) ultrasonography, cerebrovascular reactivity (CVR) was evaluated with a breath-holding test, in addition to the mean blood flow velocity (MFV), pulsatility index (PI), and resistance index (RI) of the middle cerebral artery. *Results:* After adjusting for covariates such as age, education, WMH severity, and vascular risks, TCD parameters such as MFV, PI, and RI did not differ between the 3 groups. However, CVR was significantly reduced in the AD group (45.33 ± 11.49%), compared with the other groups (56.36 ± 14.65%, controls; 53.84 ± 15.47%, MCI group; $P < .001$). Multiple regression analyses also showed that CVR was associated with MMSE scores. CVR differed according to the CDR scores ($P < .001$). *Conclusions:* Our finding may be suggestive of an underlying microangiopathic mechanism in AD patients. Furthermore, there was an association between the impaired function of cerebral microvessels and cognitive impairment. Further research is needed to fully establish whether altered cerebral hemodynamics may be considered an independent factor in predicting cognitive decline or an effect of pathologic processes involved in AD. **Key Words:** Transcranial Doppler—cerebral vasoreactivity—Alzheimer's disease—old adults.

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Received December 23, 2014; revision received January 26, 2015; accepted January 29, 2015.

This study was supported partly by a grant from the Eisai Korea Inc.

The authors have no competing interests.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.01.031

Changes in cerebrovascular structure and functions contribute to cognitive impairment in aging and dementia.[1,2] In addition to vascular dementia, several epidemiologic and imaging studies have provided evidence supporting the vascular pathogenesis of Alzheimer's disease (AD),[3-9] which is considered as a pure neurodegenerative dementia. These studies have suggested that vascular risk factors directly reduce cerebral perfusion to a critical level of dysfunction, enhancing neuronal death in AD.[10-13] Chronic cerebral hypoperfusion could affect the brain cellular health and the development of neurodegenerative pathologies.[14,15]

Transcranial Doppler (TCD) ultrasonography is a noninvasive and inexpensive technique for evaluating cerebral hemodynamics. It is widely accepted that examination of blood flow velocity in the intracranial arteries

and its changes during different challenge tests (eg, CO_2 and acetazolamide), evaluated by TCD ultrasonography, provide a good assessment of the status of cerebral blood flow.[16,17] TCD methods are used to assess functional cerebrovascular contributions to cognitive impairment in dementia and aging and may help in the differentiation of dementia from normal aging. Decreased mean flow velocity (MFV), increased pulsatility index (PI), and decreased cerebrovascular reactivity (CVR) in the middle cerebral artery have been reported in AD patients.[14,18-22] A recent population-based study using TCD ultrasonography strongly supports this hypothesis by demonstrating that cerebral hypoperfusion precedes and possibly contributes to the onset of clinical dementia.[14] Another study has suggested that CVR is a significant predictor of cognitive decline in AD patients.[23]

However, there are few reports on patients with mild cognitive impairment (MCI). To our knowledge, to date, no study has assessed all TCD parameters such as MFV, PI, resistance index (RI), and CVR in subjects with normal cognition, those with MCI, and those with AD. Moreover, the differences in these parameters according to dementia severity, evaluated using the clinical dementia rating (CDR) scale, are still unclear.

To compare hemodynamic changes related to cerebral blood flow and vascular resistance in older adults with a wide spectrum of cognitive impairments, we assessed MFV, PI, RI, and CVR by using TCD ultrasonography in older adults with very mild-to-severe AD, those with MCI, and aged controls, and the relationship between these parameters and cognitive impairment or dementia severity was evaluated.

Materials and Methods

Participants

This was a single-center observational study approved by the Institutional Review Board of The Catholic University of Korea, Bucheon St. Mary's Hospital. All participants provided informed consent. Between May 2011 and December 2012, we consecutively enrolled patients who visited the hospital's Department of Neurology clinic. A total of 194 participants were recruited, comprising 52 controls, 75 MCI patients, and 67 AD patients. Healthy older adults who requested a medical evaluation for a routine assessment of possible cerebrovascular diseases, owing to concerns related to stroke or positive vascular risk factors, were included as controls. The control participants had no cognitive complaints, and their scores on the Korean version of the mini-mental state examination (K-MMSE)[24] were more than −1.0 standard deviations (SDs) compared with age- and education-matched norms, and their CDR[25] scores were zero. Patients with MCI fulfilled the clinical diagnostic criteria for MCI.[26] All MCI patients had subjective complaints of memory loss, objective impairment in memory (−1.5 SD on a neuropsychological test of memory [Seoul verbal learning test][27]), and no significant functional decline. Criteria of the National Institute of Neurological and Communicative Disorders and the Stroke and the Alzheimer's Disease and Related Disorders Association[28] were used to diagnose probable AD. AD patients with CDR scores of 2 or 3 were excluded because they could not cooperate with breath holding, which was performed for TCD assessment of vasoreactivity.

All participants underwent physical and neurologic examinations, blood tests (ie, complete blood count, blood chemistry, vitamin B12/folate, and syphilis serology), thyroid function tests, assessment of global cognitive functioning with the K-MMSE, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain, and TCD measurements. The height and weight of the subjects were measured, and body mass index (BMI) was calculated. Participants' history of vascular risk factors (ie, hypertension, diabetes, hyperlipidemia, ischemic heart disease, stroke, and smoking) was recorded. Participants were excluded from the study if they showed large territorial infarcts or multiple lacunes on MRI, were younger than 55 years of age, had a history of diseases (other than MCI or AD) that may cause cognitive disorders, or had major psychiatric disease. Participants with a diagnosis of delirium were excluded and those unable to be assessed because of conditions such as blindness and/or deafness. Individuals with a history of alcoholism or other substance abuse or dependence within the past 10 years were also excluded. Carotid artery stenosis was defined according to the North American Symptomatic Carotid Endarterectomy Trial method,[29] and patients with carotid artery stenosis of greater than 50% lumen diameter reduction were excluded. MRA was performed in all patients to exclude the presence of intracranial artery stenosis that might interfere with the hemodynamic status.

MRI Assessment

All participants underwent 3.0-T brain MRI (Intera; Philips Medical Systems, Best, The Netherlands), including fluid-attenuated inversion recovery imaging and T1/T2-weighted imaging. The slice thickness was 5 mm without an interslice gap. The three-dimensional time-of-flight method was used as the imaging protocol of MRA. Periventricular white matter hyperintensities (WMHs) (PVHs) and deep WMHs (DWHs) were separately evaluated according to the method proposed by the Clinical Research for Dementia of South Korea study.[30] The severity of DWHs was graded according to their largest diameter, as follows: D1 (<10 mm), D2 (≥10 and <25 mm), and D3 (≥25 mm). PVHs were rated as P1 if the cap and band were less than 5 mm, P2 if the cap or band was 5 mm or greater and less than 10 mm, and P3 if the cap or band was 10 mm or greater. By