Ankle brachial index, MRI markers and cognition: The Epidemiology of Dementia in Singapore study

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Abstract
Background and aims: Previous studies showed an independent association of low ankle-brachial index (ABI) with cognitive impairment. However, the association between low ABI and cognition in the presence of both cerebrovascular disease (CeVD) and neurodegeneration is lacking. We aimed at investigating a) the association of low ABI with markers of CeVD and cortical thickness, and b) whether the association of low ABI with cognition is influenced by these markers.

Methods: Data was drawn from the Epidemiology of Dementia In Singapore (EDIS) study where all participants (n = 832) underwent neuropsychological tests and 3T brain magnetic resonance imaging (MRI) to assess CeVD markers as well as cortical thicknesses. Cognitive function was expressed as a global composite z-score and domain-specific z-scores of a comprehensive neuropsychological battery.

Results: Multivariate analyses showed low ABI to be independently associated with intracranial stenosis [odds ratios (OR): 1.51; 95% confidence interval (CI): 1.23–1.87] and lacunar infarcts [OR: 1.29; 95% CI: 1.06–1.57]. A low ABI was also independently associated with smaller cortical thickness globally [β: 0.09; 95% CI: 0.27–0.16] as well as with the limbic [β: 0.10; 95% CI: 0.03–0.17], temporal [β: 0.09; 95% CI: 0.02–0.15], parietal [β: 0.08; 95% CI: 0.02–0.15], and occipital [β: 0.09; 95% CI: 0.03–0.16] lobes. Low ABI was associated with worse performance in verbal memory [β: 0.06; 95% CI: 0.01–0.12], which became attenuated in the presence of MRI markers.

Conclusions: A low ABI is associated with MRI markers, and affects cognition in the presence of CeVD and neurodegeneration. Atherosclerosis should be targeted as a potentially modifiable risk factor to prevent cognitive disorders.

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1. Introduction

Atherosclerosis is the main cause and contributor to vascular pathophysiology, and has been associated with cognitive impairment, stroke and mortality [1]. A simple and accessible means to measure generalized atherosclerosis in population-based settings is through the ankle-brachial index (ABI) [2,3]. Several studies have shown a low ABI (<0.9) to be associated with magnetic resonance imaging (MRI) markers of cerebrovascular disease (CeVD) such as cortical infarcts, lacunar infarcts, and intracranial stenosis [4–6]. A low ABI has also been consistently linked to impaired cognition [7]. Previous data from the Epidemiology of Dementia in Singapore (EDIS)
study found a low ABI to be independently associated with poorer cognitive performance in verbal memory after adjustments for CeVD markers [6]. However, this study was small in size, of a single ethnicity, and hence may not be representative of the population at large. In addition to CeVD, neurodegeneration is a major cause of dementia characterized by brain atrophy [8] on structural neuro-imaging. Although atherosclerosis, as measured by carotid intima-media thickness, has been associated with smaller cortical gray matter volumes [9,10], the association between ABI and neurodegeneration has not been reported previously. Moreover, increasing evidence from autopsy studies has shown that the pathogenesis of cognitive impairment is due to the overlap between cerebrovascular and neurodegenerative pathologies (80%), rather than as separate entities (20%) [11]. The common mechanism underlying the two pathologies may be atherosclerosis, which thus increases the risk for cognitive impairment and dementia [12]. However, the association between low ABI and cognition is yet to be examined in the presence of both CeVD and neurodegenerative markers.

Therefore, the present study aims to investigate the association between low ABI and CeVD and neurodegenerative markers in a multi-ethnic population from the EDIS study. In addition, the present study examines whether the association of low ABI with cognition is independent of CeVD and neurodegeneration. Specific hypotheses for the present study are: a) a low ABI is associated with small, as well as large vessel CeVD, b) a low ABI is associated with markers of neurodegeneration such as cortical thickness, and c) both markers of CeVD and neurodegeneration might influence the association between low ABI and cognitive performance.

2. Materials and methods

2.1. Study population

The Epidemiology of Dementia in Singapore (EDIS) study recruited participants from the Singapore Epidemiology of Eye Disease (SEED) study, a population-based study of three major ethnic cohorts: Chinese (Singapore Chinese Eye Study [SCES]) [13], Malay (Singapore Malay Eye Study [SIMES-2]) [14], and Indians (Singapore Indian Eye Study [SINDI-2]). As part of the first phase of the EDIS study, participants in SEED who were ≥60 years old underwent cognitive screening with the Abbreviated Mental Test (AMT) and self-reported progressive forgetfulness (PF). Screen-positives were defined using the following criteria: an AMT score of ≤6 for those subjects with up to 6 years of formal education; or an AMT score of ≤8 with more than 6 years of formal education; or if the caregiver reported progressive forgetfulness [15]. Screened-positive (n = 1598) subjects were invited to participate in the second phase of the EDIS study, which included an extensive clinical and neuropsychological evaluation, along with 3T MRI neuro-imaging. Recruitment of the EDIS participants took place from August, 8th 2010 to July, 24th 2015. Ethics approval was obtained from both the Singapore Eye Research Institute and the National Healthcare Group Domain-Specific Review Board. Written informed consent was obtained from all participants prior to their participation in this study.

2.2. Demographics and cardiovascular risk factors

A demographic questionnaire was administered to obtain information on age, years of formal education, gender, ethnicity and smoking history. A history of hypertension, hyperlipidemia and diabetes was obtained during clinical examination, and verified by medical records. The following vascular risk profiles were used: hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication; diabetes mellitus: glycated hemoglobin ≥6.5% or use of anti-diabetic drugs; and hyperlipidemia: total cholesterol levels ≥4.14 mmol/L or use of lipid lowering medication. Education was categorized into ≤6 years or >6 years of formal education.

2.3. Ankle-brachial index

Ankle and brachial blood pressures were measured using a digital device (Omron HEM-7203, Japan) and Doppler ultrasound probe (Nicolet Vascular Elite 100) over the brachial, dorsalis pedis and posterior tibial arteries bilaterally, after 5 min of rest in the supine position [6]. ABI was calculated, separately for each leg, as the ratio of the higher of the two arteries (posterior tibial or dorsalis pedis) at the ankle to the higher of the right and left systolic brachial blood pressure [16]. Participants with undetectable peripheral pulsations on the Doppler ultrasound were excluded from present analyses. For the purpose of the analysis, ABI was catego- rized as >0.9 and ≤0.9 (low) [2].

2.4. Neuroimaging markers

All participants underwent 3T Siemens Magnetom Trio Tim scanner with a 32-channel head coil, stationed at the Clinical Imaging Research Center of the National University of Singapore. Those who had contraindications for MRI such as claustrophobia or metallic implants, or who could not complete the neuro-imaging procedures were excluded from present analyses. For each participant, the following MRI markers of CeVD were graded blinded to the patient characteristics:

- cortical infarcts were identified as focal lesions involving cortical gray matter with hyperintense rim on FLAIR images and center following cerebrospinal fluid intensity and loss of tissue of variable magnitude, with prominent adjacent sulci and ipsilateral ventricular enlargement [17]
- lacunar infarcts were defined as lesions involving the subcortical regions, 3–15 mm in diameter, with low signal on T1-weighted image and FLAIR, a high signal on T2-weighted image, and a hyperintense rim with a center following cerebrospinal fluid intensity [17]. Lacunar infarcts were distinguished from perivascular spaces by the absence of a hyperintense rim and lesion following the shape of the vessel [13]
- cerebral microbleeds were defined as focal, rounded lesions of hypointensity graded on Susceptibility Weighted Images (SWI) using the Brain Observer Microbleed Scale (BOMBS) [18]
- cortical microinfarcts (CMI) were defined as hypointense lesions on T1-weighted images, <5 mm in diameter, restricted to the cortex and perpendicular to the cortical surface and confirmed on FLAIR and T2-weighted images [15]
- intracranial stenosis was graded on Magnetic Resonance Angiography (MRA) and was defined as stenosis ≥50% in the internal carotids, vertebral, basilar, posterior cerebral, middle cerebral and/or anterior cerebral arteries [19].

Quantitative MRI analyses were performed in collaboration with the Department of Radiology and Medical Informatics, Erasmus University Medical Center, Netherlands. For each participant, the following MRI markers of cortical thickness and volumes were computed:

- cortical thickness was calculated using a model based automated procedure (FreeSurfer, v.5.1.0) on T1-weighted images (TR = 7.2 ms, TE = 3.3 ms, matrix = 256 × 256 × 180 mm³). Cortical thickness was measured at each vertex by taking the
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