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Homocysteine, progression of ventricular enlargement, and cognitive decline: The Second Manifestations of ARTerial disease-Magnetic Resonance study

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Abstract

Background: Homocysteine may be a modifiable risk factor for cognitive decline and brain atrophy, particularly in older persons. We examined whether homocysteine increased the risk for cognitive decline and brain atrophy, and evaluated the modifying effect of age.

Methods: Within the Second Manifestations of ARTerial disease-Magnetic Resonance study—a prospective cohort study among patients with atherosclerotic disease—longitudinal analyses were performed in 663 patients (mean age: 57 ± 9 years; follow-up: 3.9 ± 0.4 years). At baseline and follow-up, brain segmentation on magnetic resonance imaging was used to quantify relative (%) cortical, ventricular, and global brain volumes, and *z*-scores of memory and executive functioning were calculated. Linear regression analysis was used to estimate associations of homocysteine (per standard deviation increase) and hyperhomocysteinemia (HHCY) with brain volumes, memory, and executive functioning at follow-up, adjusted for baseline brain volume, memory, and executive functioning, respectively, and age, sex, and vascular risk factors. Furthermore, interaction terms between homocysteine and age (continuous) were added.

Results: Significant interactions were observed between total plasma homocysteine (tHcy) and age with cortical, ventricular, and global brain volume (for all three measures: $P < .05$), and between HHCY and age with executive functioning ($P = .04$), and results were stratified by age. In patients aged ≥65 years, increasing tHcy level and HHCY were significantly associated with progression of ventricular enlargement (B = 0.07%, 95% confidence interval [CI]: 0.01% to 0.13% and B = 0.16%, 95% CI: 0.01% to 0.31%, respectively) and with a decline in executive function (B = −0.29, 95% CI: −0.54 to −0.04 and B = −0.84, 95% CI: −1.37 to −0.32, respectively).

Conclusion: Elevated tHcy was related to progression of ventricular enlargement and increased the risk for a decline in executive functioning in older persons.

Keywords: Homocysteine; Cognition; Executive function; Brain atrophy; Magnetic resonance imaging

1. Introduction

Due to the aging population, dementia will become one of the major health problems in the near future [1]. Early recognition of those at risk could help to identify patients for preventive treatment. Cognitive impairment and brain atrophy are commonly used as early markers of dementia [2,3]. Consequently, there is a need to identify potentially modifiable risk factors for cognitive impairment and brain atrophy. Homocysteine—an amino acid formed during methionine metabolism—may be such a risk factor, as it is associated with cognitive impairment, brain atrophy, and

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dementia [4–8]. Moreover, homocysteine levels can be decreased by folic acid, vitamin B6, and B12, and therefore could be a potential target for therapy [9].

Many cross-sectional and several longitudinal studies examined whether increased homocysteine levels were associated with cognitive impairment. Although not all, most showed a positive association [4,10–12]. It is thought that brain atrophy may be an intermediate in the association [4]. Cross-sectional studies found that an increased total plasma homocysteine (tHcy) is associated with decreased total brain volume, hippocampal volume, and cortical volume, and increased subcortical volume [7,8,13,14]. Yet, only one prospective study examined the association between tHcy and progression of brain atrophy [15], and no study examined both progression of brain atrophy and cognitive decline.

We aimed to examine the prospective association of plasma homocysteine with progression of global and cortical brain atrophy and ventricular enlargement, using automated quantitative brain volume measurements, in persons with symptomatic atherosclerotic disease. Further, we examined the prospective association of homocysteine with risk for cognitive decline.

2. Materials and methods

Data were used from the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, a prospective cohort study aimed to investigate brain changes on magnetic resonance imaging (MRI) in 1309 independently living patients presenting with symptomatic atherosclerotic disease [16,17]. In brief, from 2001 to 2005, all patients newly referred to the University Medical Center Utrecht with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease, or an abdominal aortic aneurysm (AAA) and without magnetic resonance (MR) contraindications were invited to participate. During a 1-day visit to our medical center, an MRI of the brain was performed, in addition to a physical examination, ultrasonography of the carotid arteries, and blood and urine sampling. Risk factors, medical history, and functioning were assessed with questionnaires that the patients completed before their visit to the medical center. Neuropsychological testing was introduced in the SMART-MR study starting in January 2003 and was performed on the same day as the MRI and other investigations.

From 2006 to 2009, all participants still alive were invited for follow-up, including an MRI of the brain and neuropsychological testing. In total, 754 individuals of the surviving cohort (61% of n = 1238) gave written informed consent and participated at follow-up. The SMART-MR study was approved by the ethics committee of our institution, and written informed consent was obtained from all participants.

2.1. MRI protocol

At baseline and follow-up, the MR investigations were performed on a 1.5-T whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, The Netherlands). The protocol consisted of transversal T1-weighted (repetition time [TR]/echo time [TE]: 235/2 ms; flip angle, 80°), T2-weighted (TR/TE: 2200/11 ms and 2200/100 ms; turbo factor, 12), fluid-attenuated inversion recovery (FLAIR) (TR/TE/inversion time: 6000/100/2000 ms), and inversion recovery (TR/TE/inversion time: 2900/22/410 ms) sequences (field of view, 230 × 230 mm; matrix size, 180 × 256; slice thickness, 4.0 mm; no gap; 38 slices).

2.2. Brain segmentation

We used the T1-weighted gradient-echo, inversion recovery sequence and FLAIR sequence for brain segmentation. The probabilistic segmentation technique has been described elsewhere [18,19], and has been proven to be very reliable, with similarity indices exceeding 0.8 for all segmented tissue and cerebrospinal fluid (CSF) volumes, indicating an excellent agreement between the results of the segmentation program and manual segmentation. Two preprocessing steps were performed. The first step was an intrapatient rigid registration to compensate for motion and scan variations [20]. The second preprocessing step was an automatic skull-stripping of the T1 image [21] to define a proper region of interest for the segmentation process. The actual segmentation of the MR images was performed by k-nearest neighbor classification [19]. The result of the classification method is a probability value for each voxel that quantifies the amount of a specific tissue type contained in that voxel. Total volumes were calculated by adding all probabilities and multiplying this sum with the volume of 1 voxel. The segmentation program distinguishes gray matter, white matter, sulcal and ventricular CSF, and lesions. The results of the segmentation analysis were visually checked for the presence of infarcts and adapted, if necessary, to make a distinction between white matter lesions (WMLs) and infarct volumes. Total brain volume was calculated by summing gray matter, white matter, WML, and infarct volumes. Total intracranial volume (ICV) was calculated by summing the total brain volume and the volumes of the sulcal and ventricular CSF. The brain volumes used for this analysis were brain parenchymal fraction (BPF), cortical gray matter fraction (GMF), and ventricular fraction (VF), as indicators of global, cortical, and subcortical atrophy (ventricular enlargement). All brain volumes were normalized for ICV.

2.3. Brain infarcts and WMLs

At baseline and follow-up, the whole brain was visually searched for infarcts by an investigator and a neuroradiologist. Discrepancies in rating were re-evaluated in a consensus meeting. Raters were blinded to all clinical information. Infarcts were defined as focal hyperintensities of at least 3 mm diameter on T2-weighted images. Hyperintensities located in the white matter also had to be hypointense on