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Homocysteine and pulsatility index in lacunar infarction

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ABSTRACT

Objective: To evaluate an association between plasma concentration of total homocysteine (tHcy) and pulsatility indexes (PIs) of cerebral arteries in patients with lacunar infarction (LI), comparing control subjects.
Methods: Consecutive patients referred to a neurovascular ultrasound laboratory were evaluated from March 2007 to February 2008. LI was determined by high signal intensity lesion (<15 mm) in brain MRI and PI was defined as (peak-systolic velocity – end-diastolic velocity)/mean flow velocity as recommended. Plasma tHcy was categorized into tertiles and analyzed for an association with PIs.
Results: 83 patients with LI and 135 control subjects were analyzed. The patients with LI showed significantly lower peak-systolic, end-diastolic, and mean flow velocities than the control group, especially in posterior circulatory beds. The group with LI showed independent associations between the higher tertiles of tHcy and the graded and linear increases of PIs, even after adjusted for potential confounders including vascular risk factors, but not in the control group. Interaction terms were significant in both the right middle cerebral artery and basilar artery, and borderline significant in the left vertebral artery ($p = 0.040$, 0.022, 0.055, respectively).
Conclusion: Increased plasma tHcy was significantly and independently associated with increased cerebral arterial resistance in the patients with LI.

1. Introduction

Lacunar infarction (LI) is unique in both characteristic neuroimaging findings and clinical symptomatology [1]. Although LI has been accepted as a benign disease, studies on a long-term prognosis showed that LI also should be treated carefully like other major vascular diseases of a grave prognosis [2]. Moreover, the related vascular risk factors of LI such as hypertension, smoking, and type 2 diabetes mellitus (DM), were somewhat different from those for large artery diseases. The risk factors of LI could be closely associated with lipohyalinosis and microatherosclerosis [3].

LI has been reported to show an independent association with increased plasma concentration of total homocysteine (tHcy) [4,5]. A recent meta-analysis showed that the increased tHcy was a modifiable vascular risk factor reporting a significant reduction of ischemic stroke or coronary heart disease with Hcy-lowering therapy consisting of B vitamins [6]. Homocysteine (Hcy) is a naturally occurring amino acid, producing DNA, steroid hormones, and some proteins. Hcy, however, was closely related with endothelial dysfunction and extracellular matrix proliferation, eventually causing arterial luminal reduction [7]. Considering the fact that LI usually had no definite arterial steno-occlusive lesions, the pathogenic effect of an increased tHcy on arterial resistance seemed to be reasonably matched to the etiopathogenesis of LI.

PI by transcranial Doppler (TCD) examination was reported as an independent predictor of small vessel disease [8] as well as cerebral infarction [9]. PI reflects downstream arterial resistance [10]. Although PI was found to increase in small vessel diseases and LI, it is not clear yet whether the elevated PI could also be associated with an increased tHcy in patients with LI. Thus, the objective of the present study was to investigate an association between tHcy and pulsatility indexes (PIs) of cerebral arteries like middle cerebral artery (MCA), basilar artery (BA), and vertebral artery (VA) in patients with LI and control subjects.

2. Subjects and methods

2.1. Study population

All subjects referred to the Neurovascular Ultrasound Laboratory in stroke centre of Chonbuk National University Hospital, South Korea were recruited from March 2007 to February 2008.

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The present study design and its population were described previously in detail [11]. In brief, all acute ischemic strokes were categorized originally into five groups; large artery atherothrombosis (LAA), cardioembolism (CE), small vessel occlusion (SVO) or lacunar infarction (LI), and stroke of determined etiology (SDE), and undetermined etiology (SUE) as recommended by the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study [12]. The patients with LI were defined as having typical clinical symptoms and relevant lesion on a diffusion-weighted image of brain magnetic resonance image (MRI) [1]. The definition of brain MRI for LI was a lesion less than 15 mm in diameter, with a high signal intensity on diffusion-weighted image and a low signal on apparent diffusion coefficients. The lesion in brain MRI should be relevant to clinical symptoms for lacunar syndromes. The control group was defined as patients with vascular risk factors but no previous history of vascular diseases like stroke, myocardial ischemia, and peripheral vascular disease. For the present analysis, steno-occlusive lesions in the internal carotid artery were determined if a patient had more than 50% luminal narrowing in at least one of internal carotid arteries according to the method recommended by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [13]. Subjects with ICA steno-occlusive lesions were excluded from this study. The present study was performed with the approval of the institutional ethics committee at the author's institution and all participating patients gave written informed consents at the time of TCD examination.

2.2. Assessments and measurements

The present study collected the prior history of cardiovascular disease, type 2 diabetes mellitus (DM), hypertension, dyslipidemia, and medication usage from consecutive patients and control subjects. Smoking status was classified into three categories: current smokers, ex-smokers, and non-smokers. Patients with a persistent elevation of blood pressure (i.e., $\geq$140/90 mmHg) or taking antihypertensive medications were classified as hypertensive according to the criteria defined by the seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure [14]. Subjects with type 2 DM were those who reported having been told by a physician that diabetes was present or those with fasting blood glucose of greater than 6.9 mmol/L more than 2 times according to the criteria defined by the American Diabetic Association [15]. Dyslipidemia was defined as the ones having a total cholesterol greater than 6.2 mmol/L, triglyceride greater than 2.3 mmol/L, or LDL cholesterol greater than 4.1 mmol/L as recommended [16].

Plasma total homocysteine (tHcy) was measured by fluorescence polarization immunoassay (AxSYM, Abbott Laboratories, Abbott Park, IL). The patients with LI had tHcy measurements in the third day after the onset of acute ischemic stroke, while the control subjects had the measurements at the date of TCD examination. All other laboratory data used in the present study were measured on the same day as the TCD examination was conducted. Blood samples were drawn in the morning after a 12-h overnight fast and assessed with a Hitachi 7600-110 analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan). The level of free T4 (FT4) in serum was determined by electrochemiluminescence immunoassay with Elecsys 2010 (Roche Diagnostics, GmbH, Mannheim, Germany). Daily quality control of the above measurements made on the Hitachi analyzer was carried out by duplicate measurements with a commercially available control material (Bio-Rad Laboratories, Hercules, CA). The coefficient of variation (CV) resulting from intra-assay precision experiments for tHcy was between 4.4 and 1.3% at concentrations ranging from 6.5 to 26.8 μmol/L. The CV of inter-assay imprecision in the same concentration range was between 2.1 and 4.9%.

2.3. Transcranial Doppler (TCD) examination

Blood flow velocities at both right and left middle cerebral arteries (MCA), basilar artery (BA), and both right and left vertebral arteries (VA) were measured using SONARA/tek 5.18B with 2 MHz hand-held transducer. For consecutive control subjects and patients with the diagnosis of subacute (3–14 days from) LI referred to the Neurovascular Ultrasound Laboratory of CNU hospital, the complete diagnostic spectral TCD examination was conducted [17]. Specific methods for TCD measurement and interpretation used in the study were explained previously in detail [11].

Pulsatility index (PI) was used as a reflection of impedance to flow distal to the point of sampling [18]. PI was automatically calculated by the TCD instrument using the following definition (peak systolic velocity [PSV] − end diastolic velocity [EDV])/mean flow velocity [MFV]. All PSVs, EDVs, and MFVs were measured along the full segments of each cerebral artery as recommended [17]. The velocity data used in the present study were those calculated and displayed automatically by the TCD device. In the present study, however, only the PIs and velocities at the most proximal segment of each artery (i.e., M1 proximal segment for MCA, at 50–60 mm depth; proximal BA at 75–80 mm depth) were selected, because the PIs at the most proximal segment of each cerebral artery were thought to represent the arterial resistance of the relevant distal arterial beds.

3. Statistical analysis

The descriptive data for the major characteristics were expressed as a mean ± standard deviation (SD) or percentage as appropriately. An independent *t*-test was used to determine the statistical differences in the continuous variables, whereas a chi-square test was used for categorical variables. A general linear model was used for all intracranial arteries to evaluate the linear relationship between adjusted PIs and tHcy level categories (tertiles) in the two groups separately. Bonferroni tests were applied to correct for multiple comparisons. Interaction terms in each intracranial artery were created like groupings (control vs. LI) × tertiles of tHcy for PI, and their significances were assessed. All statistical analyses were conducted using SPSS software version 16.0 (SPSS, Chicago, IL).

4. Results

In total, 549 patients were referred to the Neurovascular Ultrasound Laboratory in CNU hospital for the aforementioned one-year period. About 158 patients (28.8%) were free from both stroke and other vascular diseases. In the remaining 391 patients (71.2%) who had ischemic strokes, 86 patients (15.7%) had LI. 23 (4.2%) and 3 (0.5%) out of the 158 controls and 86 LI patients, respectively, were diagnosed as having proximal ICA steno-occlusive lesion, and thus, excluded from the present study. Finally, 135 (24.6%) and 83 (15.1%) were included as the control and the patients with LI, respectively, in the present study.

Age, hematocrit, and FT4 were not different between the two groups, as shown in Table 1. The proportion of women was higher in the control group with a borderline significance. As for the risk factors, the proportions of smoker and hypertension were significantly higher in the LI group, and type 2 DM also showed a higher proportion in the LI group than the control group, but was not significant. The proportion of dyslipidemia and the plasma concentration of tHcy and its distribution of tertiles were not different between the two groups.

TCD accessibilities were not different between the two groups either, but somewhat lower in both MCAs than in BA as well as in