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The relationship between leukoaraiosis volume and parameters of carotid artery duplex ultrasonographic scanning in asymptomatic diabetic patients

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ABSTRACT

The significance of asymptomatic leukoaraiosis is unknown although cerebral microangiopathy is regarded as its pathology. To confirm the relationship between leukoaraiosis and cerebral microangiopathy, the pulsatility index (PI) at the cervical internal carotid artery (CA) which has been proposed as an indicator of microangiopathy, was evaluated in relation to leukoaraiosis. With 122 asymptomatic diabetic patients, leukoaraiosis volume was calculated with magnetic resonance imaging and its correlation with age, microalbuminuria and parameters of extracranial CA duplex ultrasonographic scanning were analyzed. The leukoaraiosis volume correlated with PI on the right side ($p = 0.027$), and intima-media thickness on the left ($p = 0.017$). However multivariate analysis indicated that age alone was a significant independent factor, positively correlating with leukoaraiosis volume on both sides ($p < 0.0001$ on both sides). The underlying pathology of leukoaraiosis should be multifactorial. Further exploration is necessary to distinguish "ischemic" and "non-ischemic" leukoaraiosis.

1. Introduction

The patchy white matter hyper-intensity areas displayed on T2-weighted brain magnetic resonance imaging (MRI), known as leukoaraiosis, are well known to increase with age [1–3]. As leukoaraiosis is frequently seen in patients with stroke [4], dementia [5], or hypertension [2], this radiological finding may be pathologically significant. Generally, the underlying disorder is thought to be related to the vasculature [6], including small intraparenchymal cerebral arteries or arterioles [7]. These small cerebral vessels are anatomically similar to kidney vessels [8] and impaired kidney function is reportedly related to leukoaraiosis volume [9]. By comparing the pulsality index (PI) with microalbuminuria, which is the parameter of renal microangiopathy, we previously proposed that PI measured at the cervical internal carotid artery (CA) can also be used as a parameter of microangiopathy, and may more accurately reflect cerebral microangiopathy than microalbuminuria [10]. An increase in the resistance of cerebral circulation due to cerebral microangiopathy may result in a higher PI at the cervical internal CA. We hypothesize several parameters measured by extracranial CA duplex ultrasound scanning (ECADUS) including PI, may correlate with leukoaraiosis, assuming its pathological basis in the small cerebral vessels. We investigated the relationship between leukoaraiosis volume and microangiopathies in asymptomatic diabetic patients, using several exclusions to decrease the biases for leukoaraiosis volume. Leukoaraiosis was measured employing volumetric analysis with which concise statistical analysis could be made [11].

2. Materials and methods

2.1. Study population

After the approval of our cross-sectional study protocol by the Institutional Review Board of National Hospital Organization Okayama Medical Center in December 2005, the clinical data of patients who were admitted to our hospital for a "diabetes hospitalization program" were collected in a prospective manner. The aim of the "diabetes hospitalization program" is to examine diabetes complications and to determine the adequate maintenance dose of medication. The criteria for entering this program are a 2 h postprandial plasma glucose concentration of 200 mg/dl or higher and a hemoglobin A_{1C} value of 7.0% or higher. Any patients who have clinically acute symptoms such as angina, myocardial infarction, stroke, or infection are excluded. Head MRI with MR angiograms

Abbreviations: CA, carotid artery; ECADUS, extracranial carotid artery duplex ultrasound scanning; EDV, end diastolic velocity; FLAIR, fluid-attenuated inversion recovery; IMT, intima-media thickness; MRA, magnetic resonance angiograms; MRI, magnetic resonance imaging; PI, pulsatility index; PSV, peak systolic velocity; u-ACR, urine albumin-to-creatinine ratio.

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(MRA), ECADUS, and the urine albumin-to-creatinine ratio (u-ACR) are examined during hospitalization.

Since our cross-sectional study aims to determine the relationship between leukoaraiosis volume on MRI and other values including parameters of ECADUS, patients with factors that could possibly bias these relationships were excluded. These exclusion factors included; (1) a history of cerebrovascular disease; (2) intracranial cerebral arterial stenosis, defined as a more than 50% stenotic diameter on each intracranial internal CA, or M1 portion of middle cerebral artery determined by MRA or extracranial cervical carotid arterial stenosis on ECADUS determined with B-mode imaging; (3) other intracranial abnormalities, including intracerebral hemorrhage scars, contusional scars or brain tumors; (4) cardiac functional abnormalities; and (5) severe renal diseases with macroalubuminuria, defined as a u-ACR $\geq$300 μg/mg, or with impaired glomerular filtration, defined as a 24 h creatinine clearance $\geq$30 ml/min/1.73 m^2. In this study, the patients with asymptomatic ischemic changes in the basal ganglionic regions were not excluded. Between January 2006 and August 2007, 122 patients with type 2 diabetes were enrolled into this study.

2.2. Evaluated parameters

The parameters routinely examined with ECADUS at our institute are the peak systolic velocity (PSV), end diastolic velocity (EDV), and the PI of the bilateral common, cervical internal and external CAs and the bilateral vertebral arteries. The PI is the velocity ratio, obtained from the difference between PSV and EDV divided by the mean velocity. With B-mode imaging data, the intima-media thickness (IMT) of both common CAs and the diameter of the common and cervical internal CAs are also measured. Details of ECADUS by our institute have been described previously [12,13]. The ECADUS examinations were performed using a Powervision 8000 scanner (Toshiba Medical Systems, Tokyo, Japan) by a single technician and confirmed by one of the authors (T.T.). In our institute, B-mode and color flow images are obtained in longitudinal and transverse planes, and the IMT of the common CA was obtained 2–3 cm proximal to the dilatation of the carotid bulb. Doppler velocity spectra are recorded with the angle of insonation as close to 60° as possible, and the velocities at the internal CA are obtained 1–2 cm distal to the tip of the flow divider. Among these parameters, the values of PSV, EDV and PI of bilateral cervical internal CAs and IMT of bilateral common CAs were extracted. We also reviewed each patient's hypertension and dyslipidemia status at the time of ECASUS, as indicated by a history of taking any medications for these disorders or equivalent conditions, even those not yet treated. Smoking behavior was also reviewed and the patient was considered to have smoking history if he had smoked more than 100 cigarettes in his lifetime. As a parameter of microangiopathy, the presence of microalbuminuria, which was defined as 30 μg/mg $\leq$ u-ACR < 300 μg/mg, was also recorded from the laboratory data at admission. These parameters and the age at admission were analyzed in relation with the leukoaraiosis volume on MRI.

2.3. Volumetric analysis of leukoaraiosis

MRI of the brain was performed with a 1.0 T GE Excite scanner (GE Healthcare, Milwaukee, Wis). The protocol of MRI for the patients on the "diabetes hospitalization program" included axial T1-weighted, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. Furthermore MRA of the brain were also taken to evaluate the intracranial cerebral arterial stenosis. The MRA was taken on the 3D time-of-flight technique (TR/TE, 31/3.2 ms; flip angle, 20°; 1.2 mm section thickness; 224 × 128 matrix size; 16 cm field of view). For volumetric analysis, we used the raw data of FLAIR images, which were obtained using the same protocol (TI/TE/TR, 2000/120/8000 ms; 6 mm section thickness with 1.2 mm spacing between sections; 256 × 160 matrix size; 24 cm field of view) for all study participants. Using nine axial slices, white lesions in the parenchyma were regarded as leukoaraiosis and signal intensities higher than a set threshold were considered to be within the area of leukoaraiosis. The high signal intensities from the midline and the scalp were excluded. Signal intensities above a set threshold were measured using Scion Image for Windows, beta 4.0.2 version. The leukoaraiosis volume was obtained from the sum of the leukoaraiosis areas from nine slices by multiplying by 7.2 mm, which was the thickness of one slice. To determine a threshold level that is most comparable to the actual clinical situation, we calculated the leukoaraiosis volume using three different thresholds; 260, 280 and 300 for 72 randomly-assigned patients (Fig. 1). Statistical comparison was performed with the qualitative analysis on Fazekas grading [14]. On Fazekas grading, deep white matter lesions were scored as 0 points for "absence", 1 for "puctate foci", 2 for "beginning confluence of foci" and 3 for "large confluent area". Periventricular lesions were scored as 0 points for "absence", 1 for "caps or pencil-thin lining", 2 for "smooth halo" and 3 for "irregular periventricular lesions extending into deep white matter". The scores of deep white matter and periventricular lesions were summed separately on each side, so that the score varied from 0 to 6 points. This score was used for the statistical analysis mentioned below and the most adequate threshold was adopted in this study.

2.4. Statistical analyses

We correlated the calculated leukoaraiosis volume at each threshold level to the Fazekas grading score, using the Spearman's correlation coefficient, and used the best correlated threshold level

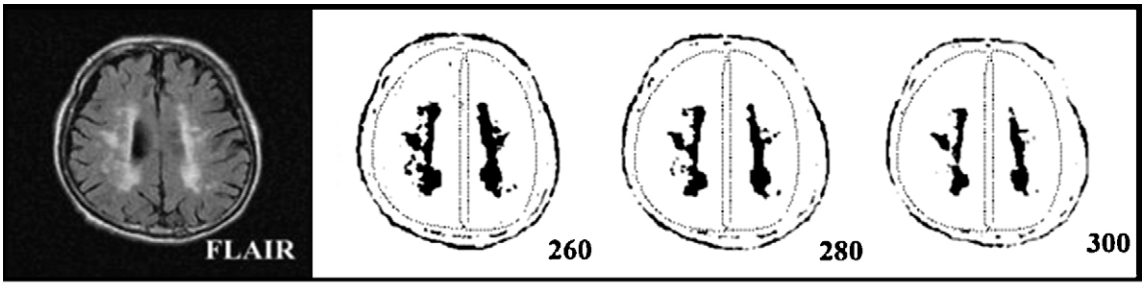

Fig. 1. FLAIR MRI and converted black-and-white images with three different thresholds. On FLAIR image, Fazekas grading score is 4 points on both sides; 2 points (beginning confluence of foci) on deep white matter lesions and 2 points (smooth halo) on periventricular lesions (A). Leukoaraiosis area is measured from converted images. The area is 215.3 mm^2 on the right side, 190.0 mm^2 on the left at the threshold of 260 (B), 159.6 mm^2 on the right, 149.1 mm^2 on the left at 280 (C) and 120.1 mm^2 on the right, 119.2 mm^2 on the left at 300 (D), respectively. Leukoaraiosis volume is calculated based on these areas.