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Liver fibrosis assessed with transient elastography is an independent risk factor for ischemic stroke

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ABSTRACT

Background and aims: The relationship between liver fibrosis and the occurrence of ischemic stroke is unknown. We investigated the correlation between liver fibrosis assessed with transient elastography (TE) and the risk of ischemic stroke.

Methods: Between April 2013 and August 2014, patients with acute ischemic stroke and subjects who underwent a health check-up were included in the study. Liver fibrotic burden was assessed with TE in all participants. The degree of liver fibrosis was compared between groups by using various multiple logistic regression models and propensity-score matched analyses.

Results: Two hundred ninety-five patients with ischemic stroke (stroke group) and 1942 subjects with health check-up (control group) were included. The mean liver stiffness (LS) on TE (5.6 *vs.* 4.1 kPa) and the proportion of significant fibrosis (>8 kPa) (9.2% *vs.* 1.8%) were significantly higher in the stroke than in the control group (all $p<0.05$). These trends were observed regardless of body mass index, the degree of hepatic steatosis, and metabolic syndrome (all $p<0.05$). The adjusted odds ratio (OR) for ischemic stroke was 1.268 (95% confidence intervals [CI] 1.183−1.358) per 1 kPa increase and 12.033 (95% CI 5.180−27.948) for significant fibrosis, compared with no fibrosis (all $p < 0.05$). Propensity-score matched analysis also confirmed that liver fibrosis was independently associated with the risk of ischemic stroke (OR 1.804 [95% CI 1.461−2.230] per 1 kPa increase, 13.184 [95% CI 3.127−55.645] for significant fibrosis, compared with no fibrosis; all $p<0.001$).

Conclusions: The degree of liver fibrosis, assessed with TE, was significantly associated with the risk of ischemic stroke.

1. Introduction

Stroke is the leading cause of death and disease burden worldwide [1]. The development of stroke is dependent on the burden of vascular risk factors, physical inactivity, and dietary pattern [2]. The cerebrovascular pathology also can be affected by diseases of other organs, such as chronic kidney disease or chronic obstructive pulmonary disease, independent of shared risk factors [3,4]. In addition, it has been recently proposed that nonalcoholic fatty liver disease (NAFLD) can be a risk factor for cardiovascular events including stroke [5–7].

Liver fibrosis is the accumulation of extracellular matrix proteins and occurs in most types of chronic liver diseases. For assessing liver fibrosis, liver biopsy has been considered as the gold-standard diagnostic technique. Recently, ultrasound-based transient elastography (TE; FibroScan; EchoSens, Paris, France) has been proposed as the surrogate to liver biopsy because of to its noninvasiveness, high accuracy, easy feasibility, and high reproducibility [8,9]. In addition, previous reports using TE showed liver fibrosis was associated with atherosclerosis in carotid and coronary arteries in patients without apparent evidences of liver disease

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[10,11]. Thus, considering the possible linkage between liver fibrosis and vascular diseases, the risk of ischemic stroke can be related with the degree of liver fibrosis. However, there is no data on the association between the risk of stroke and the degree of liver fibrosis measured by TE.

In this study, we investigated whether fibrotic burden assessed with TE, is associated with an increased risk for ischemic stroke in comparison with apparently healthy subjects without a history of ischemic stroke.

2. Materials and methods

2.1. Participants

This study retrospectively included patients with acute ischemic stroke and subjects who received a comprehensive medical health check-up. This study was approved by the institutional review board of Severance Hospital, Yonsei University Health System. Informed consent was waived owing to the retrospective nature of the study.

Consecutive patients with acute cerebral infarction or transient ischemic attack within 7 days after symptom onset who were admitted to Neurology Department of the Severance Stroke Center, Yonsei University, Seoul, Korea, between January 2014 and October 2014, were considered eligible for this study. During admission, all patients were thoroughly evaluated to determine their demographic data, medical history, clinical manifestations, and vascular risk factors. Systemic investigations were performed in every patient, including 12-lead electrocardiography, standard blood tests, and brain CT and/or magnetic resonance imaging (MRI) with angiographic studies.

Control subjects were included from participants who underwent a comprehensive medical health check-up between January 2014 and August 2014 at Severance Check-up Center Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. During the health check-up, the subjects underwent a comprehensive evaluation, including TE, for hidden vascular risk factors, vascular diseases, and liver disease.

2.2. TE assessment

All participants underwent TE with an M probe. TE was performed on the right lobe of the liver through the intercostal space with the participant lying in the dorsal decubitus position with the right arm in maximal abduction. One experienced technician at each center, blinded to the clinical information of participants, performed the TE examinations. All TE examinations were performed at least 10 times, between the 5th and 7th intercostal spaces, at the mid-to-anterior axillary line [12]. The TE results for the degree of liver fibrosis were expressed as kilopascals (kPa) for liver stiffness (LS). The median value of successful measurements was selected as the representative of LS values for a given participant. As an indicator of variability, the ratio of the interquartile range (IQR) to the median of LS values was calculated. LS measurement failures were defined as the absence of valid shots (i.e., valid shots = 0). A reliable LS value was defined by using the following three criteria: (i) at least 10 valid shots, (ii) a success rate (i.e., the ratio of valid shots to the total number of shots) of at least 60%, and (iii) an IQR $\leq$30% of the median LS value. Based on previous studies [13,14], we categorized LS values into three groups: <5.6 kPa for no fibrosis, 5.6–8.0 kPa for mild fibrosis, and >8.0 kPa for significant fibrosis.

In addition to LS, controlled attenuation parameter (CAP) values, representing the degree of hepatic steatosis, were also collected. Briefly, the CAP measures the ultrasonic attenuations by hepatic steatosis at 3.5 MHz by using signals acquired by TE, and is simultaneously calculated with the LS value by using the same signals. In our study, a CAP value of >250 dB/m was defined as the presence of fatty liver [15].

2.3. Clinical and laboratory variables

We collected demographics and data on medical and laboratory results (Supplementary Methods).

2.4. Statistical analysis

Statistical analysis was performed by using the Windows SPSS package (version 20.0; IBM Corp., Armonk, NY, USA) and the SAS package (version 9.1.3; SAS Inc., Cary, NC, USA). For the comparison of the two groups, the chi-square test was used for categorical variables and independent *t*-test or Kruskal-Wallis test for continuous variables, as appropriate. Linear-by-linear test was also used for comparison of the degree of liver fibrosis between groups. To find independent factors for ischemic stroke, a multivariate logistic regression analysis was performed.

For minimizing selection bias due to substantial imbalance in baseline characteristics between the two groups, we used the propensity-score matched (PSM) analysis, which was performed for each patient with logistic regression models including age, sex, hypertension, diabetes mellitus, hypercholesterolemia, metabolic syndrome, liver enzymes, estimated glomerular filtration rate, platelet counts, and lipid profiles. For univariate analysis, categorical variables were compared with the McNemar test and continuous variables with paired *t*-tests. To identify independent factors associated with the development of ischemic stroke, a generalized estimating equation was used. Statistical significance was set at $p<0.05$.

3. Results

For this study, 295 patients for the stroke group and 1942 subjects for the control group were included (Supplementary Fig. 1). Of the patients for the stroke group, we could determine the underlying stroke mechanism based on the classification in the Trial of ORG 10172 in Acute Stroke Treatment in 274 patients with acute ischemic lesion on brain imaging. The most common stroke mechanism was cardioembolism (n = 107, 39.5%), followed by more than two causes (n = 71, 26.2%), large artery atherothrombosis (n = 35, 12.9%), negative evaluation (n = 33, 12.2%), stroke of other determined etiology (n = 14, 5.2%), and lacunar infarction (n = 11, 4.1%). Among the entire population sample (n = 2237), the mean LS and CAP value was 4.3 kPa and 243.3 dB/m, respectively. According to the predetermined definition, 62 (2.8%) participants had significant fibrosis and 922 (41.2%) had fatty liver, respectively.

3.1. Comparison between total participants in the stroke and control groups

Fig. 1 shows that the proportion of total participants considered to have a normal LS value (<5.6 kPa) was significantly higher in the control group than in the stroke group (90.6% *vs.* 69.2%, $p<0.001$), whereas the proportion of those with fatty liver was similar between the stroke and control groups (42.4% *vs.* 41.0%; $p=0.665$). Likewise, the mean LS value was significantly higher in the stroke group (mean 5.6 *vs.* 4.1 kPa, $p<0.001$), while the mean of CAP was not different between the two groups (mean 242.1 *vs.* 243.5 dB/m, $p=0.646$) (Table 1). The differences in the burden of liver fibrosis between the two groups was consistently observed regardless of

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