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Brain microangiopathy and macroangiopathy share common risk factors and biomarkers

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ABSTRACT

Aims: Besides carotid or cardiac embolism, stroke can occur via microangiopathy (small arterial disease [SAD]) and macroangiopathy (intracranial atherosclerotic stroke [ICAS]) of the intracranial vasculature. There have been efforts to identify risk factors specific to microangiopathy and macroangiopathy, including vascular risk factors, and protein and genetic biomarkers. We hypothesized that despite the anatomic and pathophysiological differences between microvessels and macrovessels, microangiopathy and macroangiopathy share common risk factors during disease progression.

Methods: Among 714 patients with acute infarctions within middle cerebral artery territory, 126 with SAD and 116 with ICAS were included in this study. Subclinical microangiopathy (degree of leukoaraiosis) and macroangiopathy (number of tandem stenosis) was graded in each patient. Inflammatory biomarkers (C-reactive protein, E-selectin, and LpPLA2), endothelial dysfunction (asymmetric dimethylarginine, urinary albumin-to-creatinine ratio, endostatin, and homocysteine), atherogenesis (lipoprotein(a), adiponectin, and resistin), and renal function (creatinine clearance and estimated glomerular filtration rate) were assessed.

Results: Compared with the patients with isolated SAD, those with isolated ICAS were younger, were current smokers, and showed higher apoB levels ($p < 0.05$ in all cases). However, with the progression of subclinical microangiopathy, asymptomatic macroangiopathy worsened and *vice versa*. No significant differences in risk factors were observed between advanced SAD and ICAS. Decreased renal function was independently associated with progression of microangiopathy and macroangiopathy. Markers of endothelial dysfunction, but not the other markers, were significantly related to creatinine clearance level.

Conclusions: Mild to moderate loss of renal function is strongly associated with both intracranial microangiopathy and macroangiopathy. Endothelial dysfunction may be associated with this relationship.

1. Introduction

Besides carotid or cardiac embolism, stroke can occur via microangiopathy (small arterial disease [SAD]) and macroangiopathy (intracranial atherosclerotic stroke [ICAS]) of the intracranial vasculature. Both are common stroke subtypes worldwide.

Numerous efforts have been made to identify the risk factors associated with intracranial microangiopathy and macroangiopathy [1]. Nevertheless, the apparent differences in risk factors between them are unclear. This could be caused by several reasons. First, the current stroke classification system may have limitations in defining intracranial microangiopathy and macroangiopathy. An autopsy study showed that intracranial atherosclerosis that was not severe was also responsible for parent territorial stroke [2]. Recently developed high-resolution magnetic resonance imaging (MRI) techniques can visualize intracranial wall plaque and provide information on the possible mechanisms of stroke [3]. Second, novel risk factors but not the conventional risk

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factors may differ between intracranial microangiopathy and macroangiopathy. Several recent studies investigated possible novel risk factors of intracranial macroangiopathy, which include metabolic syndrome and adipokines (adiponectin and resistin) [4–6], inflammatory markers [7,8], lipoprotein (a) [9,10], homocysteine [11], and endothelial dysfunction (asymmetric dimethylarginine [ADMA] and E-selectin) [6,7]. However, these biomarkers are also reported to be associated with cerebral microangiopathy [1,12].

We hypothesized that despite the anatomic and pathophysiological differences between microvessels and macrovessels, they share common risk factors because cerebral microangiopathy and macroangiopathy commonly coexist. Thus, we compared conventional and novel risk factors of stroke in patients with ICAS and SAD, in consideration of the degree of subclinical macroangiopathy (asymptomatic tandem stenosis) and microangiopathy (leukoaraiosis).

2. Patients and methods

We prospectively recruited patients with acute symptomatic infarctions within the middle cerebral artery (MCA) territory admitted to a tertiary university stroke center between October 2008 and January 2012. We defined potential participants as patients who experienced focal or lateralizing symptoms within 7 days of symptom onset and showed relevant lesions on diffusion-weighted imaging (DWI). Patients with potential sources of cardioaortic embolism, based on the modified Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST), extracranial atherosclerosis with significant (≥50%) stenosis in the relevant extracranial arteries, other stroke mechanisms (coagulopathy, vasculitis, moyamoya disease, internal carotid artery dissection, and others), or incomplete evaluations were excluded. Local institutional review boards approved this study. All the patients or patient's guardians provided informed consent with regard to participation in the study.

During the study period, 1801 patients visited our center with acute ischemic stroke or TIA. Of 714 patients with acute MCA infarctions on DWI, 242 were included in this study. According to the lesion distribution on DWI and the presence of stenosis in the relevant MCA, we divided the patients into two groups: (1) the ICAS group, patients with infarcts within the MCA territory and relevant MCA stenosis, and (2) the SAD group, patients with deep infarctions and without stenotic lesions on the relevant MCA. We have reported that patients with intracranial atherosclerosis (especially branch occlusive disease [BOD]) are often misclassified as having microangiopathy or cryptogenic cause [13,14]. Thus, in this study, we regarded any degree of intracranial artery stenosis as macroangiopathy.

2.1. Workups

We collected clinical information, including age, sex, and vascular risk factors. All patients underwent diagnostic testing that included routine blood tests, electrocardiography, at least 24 h of cardiac telemetry, and echocardiography. Our definitions of vascular risk factors were as follows: (1) Hypertension was deemed present when the patient had been undergoing treatment with antihypertensive agents or a blood pressure of either ≥160 mm Hg systolic or ≥90 mm Hg diastolic on at least 2 occasions after the acute phase of their ischemic stroke. (2) Diabetes mellitus was deemed present when the patient had been receiving medication for diabetes, had an elevated fasting glucose level ≥126 mg/dL or a 2-h plasma glucose level ≥200 mg/dL during their oral glucose tolerance test, or had a plasma glucose level ≥200 mg/dL along with classic symptoms of hyperglycemia, hypoglycemic crisis, or hemoglobin A1c level >6.5%.[8] (3) Dyslipidemia was determined to be present if the patient had been taking lipid-lowering agents or had a total cholesterol level >240 mg/dL, triglyceride level >200 mg/dL, or low-density lipoprotein cholesterol level >160 mg/dL. ApoB and apoA1 levels were determined by using nephelometry (Behring Nephelometer, Marburg, Germany). (4) Coronary artery disease was regarded as being present when the patient had angina, myocardial infarction, or a history of coronary angioplasty or coronary bypass surgery. (5) Current smokers were those who regularly smoked at least 1 cigarette per day when admitted to the center. (6) Body mass index was measured within 3 days of admissions in most patients.

In addition, creatinine clearance tests, i.e., creatinine clearance and estimated glomerular filtration rate (eGFR), were measured as markers of kidney function. Serum creatinine level was measured by using the Jaffe method with a Hitachi 7600-210 chemistry analyzer (Hitachi, Japan), and creatinine clearance was calculated according to the Cockcroft-Gault formula. eGFR was calculated by using the Modification of Diet in Renal Disease (MDRD) Study equation.

2.2. Novel biomarkers

To further evaluate the possible mechanisms of subclinical microangiopathy and macroangiopathy, the following markers were determined in patients enrolled from August 2010 to January 2012 (n = 113). Inflammatory biomarkers included high-sensitivity C-reactive protein [hs-CRP], lipoprotein-associated phospholipase A2 [LpPLA2] (a calcium-independent phospholipase-derived especially from macrophages), and E-selectin (also known as CD62E, a cell adhesion molecule expressed only on endothelial cells recruiting leukocytes to the site of injury). Biomarkers for endothelial dysfunction included ADMA (an endogenous inhibitor of nitric oxide synthase), urinary albumin-to-creatinine ratio (UACR), and homocysteine. The level of endostatin, an angiogenesis inhibitor that may suppress angiogenesis and collateral development, was measured. Atherogenic biomarkers included lipoprotein (a) (a lipid–protein complex with proatherogenic and prothrombotic properties) and adipokines (adiponectin and resistin, hormones secreted from adipose tissue). Amounts of protein in plasma were quantified by using the following enzyme-linked immunosorbent assay (ELISA) kits: human ADMA ELISA kit (Immundiagnostik, Cat No. K7828), human E-selectin ELISA kit (Biosensis, Cat No. BEK-2089-2P), human adiponectin and resistin ELISA kits (AdipoGen, Cat Nos. AG-45A-0002PP-KI01 and AG-45A-0023PP-KI01, respectively), human Endostatin ELISA kit (Raybiotech, Cat No. ELH-Endostatin-001), and human Lp-PL-A2 ELISA kit (EIAab, Cat No. E0867h). ELISAs were performed following the manufacturers' instructions. All ELISA absorbance readings were performed with reference to the standard curve. All samples were run in duplicate. ELISA plates were read by using the SpectraMax 340PC384 Microplate Reader and analyzed by using the SoftMax® Pro Data Analysis Software (Molecular Devices). Serum hs-CRP concentration was measured with the turbidimetric immunoassay by using an autochemistry analyzer (Hitachi 7600-210, Hitachi, Japan). The UACR was calculated. Plasma homocysteine levels were determined by using the method of Vester and Rasmussen [15]. Plasma lipoprotein(a) level was measured by using an immunoturbidimetric method (Roche Hitachi Modular P800, Japan). Blood samples were drawn after an overnight fast and centrifuged within 1 h after collection (mean ± SD, 3.25 ± 2.59 days after stroke onset) for blood biomarkers. Plasma was separated and frozen immediately at −70 °C until analysis.