Endothelial Function, Inflammation, Thrombosis, and Basal Ganglia Perivascular Spaces in Patients with Stroke

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Background and Objective: Recent studies suggest perivascular spaces are a marker of small vessel disease, blood–brain barrier permeability, and inflammation, but little is known about their risk factors and associations with peripheral blood markers. *Materials and Methods:* In prospectively recruited patients with recent minor ischemic stroke, we investigated the influence of age, sex, hypertension, diabetes, and smoking on the severity of perivascular spaces in the basal ganglia seen on T2-weighted magnetic resonance imaging. We assessed plasma markers of endothelial function (von Willebrand factor, intracellular adhesion molecule-1), inflammation (interleukin-6, tumor necrosis factor-alpha, C-reactive protein), and thrombosis (fibrinogen, prothrombin fragments 1 + 2, thrombin–antithrombin complex, tissue plasminogen activator, D-dimer). We used a validated semi-automated method to measure basal ganglia perivascular spaces count and volume. We tested uni- and multivariable associations between blood markers and basal ganglia perivascular spaces count and volume. *Findings:* In 100 patients (median age: 67 years, range: 37-92), on adjusted analysis, basal ganglia perivascular spaces count was associated with age (r = .117, P = .003) and hypertension (r = 2.225, P = .013). On multivariable linear regression, adjusted for age, sex, hypertension, smoking and diabetes, reduced von Willebrand factor was associated with increased basal ganglia perivascular spaces count (r = –.025, P = .032). *Conclusion:* The association of increased basal ganglia perivascular spaces count with reduced von Willebrand factor is novel. As von Willebrand factor may promote cerebral endothelial integrity, insufficient von Willebrand factor is consistent with dysfunctional cerebral endothelium and increased basal ganglia perivascular spaces in cerebral small vessel disease. Quantitative perivascular spaces measurement may increase sensitivity to detect cerebral endothelial dysfunction. **Key Words:** Endothelial function—stroke—small vessel disease—perivascular spaces.

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Received May 22, 2016; revision received August 3, 2016; accepted August 5, 2016.

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1052-3057/$ - see front matter

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http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.08.007

Introduction

Perivascular spaces (PVS), or Virchow–Robin spaces, are pial extensions of the subarachnoid space that surround the arteries, arterioles, veins, and venules as they penetrate the brain parenchyma.[1,2] PVS are an important drainage conduit for soluble and insoluble material through the central nervous system.[3] Many inflammatory processes take place in PVS; for example, PVS are a specific site for immune cell accumulation, reaction, and transmigration into the brain parenchyma (e.g., leukocytes, dendritic cells, T-cells, B-cells, and macrophages[4-6]).

PVS on magnetic resonance imaging (MRI) are an imaging marker for cerebral small vessel disease (SVD).[7-9] PVS are associated with other SVD features, such as white matter hyperintensities (WMH), atrophy, microbleeds, lacunes, and recent small subcortical infarcts.[10] Increasing numbers of PVS were also associated with increased blood–brain barrier (BBB) permeability in stroke patients,[11] worse cognitive function in older people,[12] and more WMH in older subjects[13] and in patients with stroke.[7,8]

Blood marker levels in the peripheral circulation could reflect endothelial function, inflammation, and thrombosis changes in the brain, and are associated with SVD features such as WMH and lacunar stroke.[14] However, only four studies explored the associations between blood markers and PVS.[13,15,16] More PVS in the basal ganglia (BG) regions were associated with higher plasma oxidized low-density lipoprotein in adjusted analysis, suggesting that oxidized low-density lipoprotein may contribute to PVS progression through endothelial dysfunction and antibody formation.[16] Associations between more BG PVS and higher plasma neopterin (from activated monocytes or macrophages),[15] plasma interleukin-6 (IL-6),[17] and plasma C-reactive protein[13] suggested associations with inflammation in patients with stroke,[15,16] vascular disease,[17] and older community-dwelling individuals,[13] respectively.

These studies used visual assessment of PVS that reflects the number of visible PVS, but PVS may increase in size as well as in number, and the visual score may lack sensitivity in detecting associations with plasma markers. We developed a computational quantitative method to measure PVS volume and number.[18] As it is unclear if PVS reflect primarily inflammation, endothelial dysfunction, thrombosis, or all three, in the present analysis we test associations between PVS count and volume and plasma markers of endothelial function, inflammation, and thrombosis in the chronic phase after lacunar stroke or mild cortical stroke.

Methods

Patient Recruitment and Assessment

We used data from 100 patients recruited prospectively with lacunar or minor (i.e., non-disabling) cortical ischemic stroke who participated in a study of BBB permeability.[19] All patients were carefully examined by an experienced stroke physician who recorded the full medical history and risk factors, including hypertension, diabetes, smoking, heart disease, and cholesterol. All patients had diagnostic brain MRI, including sagittal T1-weighted and axial diffusion-weighted imaging, T2-weighted, fluid-attenuated inversion recovery, and gradient-echo sequences acquired on a GE Signa scanner (General Electric Medical Systems, Milwaukee, Wisconsin, USA) at 1.5T, to classify final stroke subtype and qualitatively assess PVS (sequence details published previously[7,19]). All patients received guideline-based stroke secondary prevention (clopidogrel, statin in all, and antihypertensive drugs in patients with hypertension). All patients gave written informed consent to participate in the study and the study was approved by the local ethics committee.

MRI Data Analysis

All image processing was performed blind to clinical and blood marker details. We used a semi-automated method to measure BG PVS count and volume.[18] This method uses intensity-normalized structural T2-weighted MRI obtained after performing a linear intensity adjustment with a gamma correction factor of two, followed by linear mapping to the original images, in MATLAB (http://www.mathworks.co.uk/help/images/ref/imadjust.html). We, then, manually applied a standard region-of-interest extraction, limiting the assessment of PVS to two bilateral ovoid regions on a representative BG slice, one in each hemisphere, delineated by the vertical ramus of the lateral fissures and the posterior segment of the lateral fissures, and automatically extracted PVS using the Analyze 10.0 software (AnalyzeDirect, Inc., Overland Park, Kansas, USA). This method showed a strong relationship with visual scores, with regression coefficients of 2.114 (95% confidence interval: 1.364-2.864, $P < .001$) for BG PVS count and .022 (95% confidence interval: .012-.031, $P < .001$) for BG PVS volume.

Blood Marker Assessment

We collected venous blood from each patient approximately 2 months (minimum of 1 and maximum of 3 months) after stroke to avoid the acute stroke phase. Blood samples were put immediately into two 2.5-mL ethylenediaminetetraacetic acid tubes and an 8-mL tube containing clot activator and gel. The samples were transferred from the ward on water ice, centrifuged at 2000 g for 10 minutes, and stored at −80°C until analysis.

Blood marker analysis was performed in an accredited laboratory, blinded to the patients' clinical and imaging details. We measured 10 blood markers using high sensitive assays (assay details in Supplementary Table S1):

1) endothelial dysfunction: von Willebrand factor (vWF) and intracellular adhesion molecule-1;

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