Correlation of Plasma Vascular Endothelial Growth Factor and Endostatin Levels with Symptomatic Intra- and Extracranial Atherosclerotic Stenosis in a Chinese Han Population

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Background: Symptomatic intracranial atherosclerotic stenosis (ICAS) and extracranial atherosclerotic stenosis (ECAS) are different in many aspects. Here, we explored the association between the location or severity of atherosclerotic stenosis and pro- or antiangiogenic factors, specifically vascular endothelial growth factor (VEGF) and endostatin (ES). *Methods:* We evaluated 198 consecutive patients with acute ischemia stroke: 132 with large-artery atherosclerosis (LAA) and 66 with small-artery occlusion (small-vessel occlusion). The LAA group was subclassified into 102 patients with ICAS and 30 with ECAS. Independent associations of VEGF, ES levels, and VEGF/ES ratio with the location of cerebral stenosis and the severity or short-term prognosis (14th day modified Rankin Scale) of ICAS were evaluated. *Results:* Plasma concentrations of VEGF and ES were lower ($P < .05$) in ICAS (38.07, 32.76-46.28 pg/mL and 58.95, 55.04-59.77 ng/mL) than those in ECAS (45.00, 34.30-83.34 pg/mL and 140.74, 85.63-231.21 ng/mL). Logistic regression analysis showed that VEGF concentrations and dyslipidemia were independently associated with ICAS, with odds ratios of .987 [95% CI = (.976, .998)] and .265 [95% CI = (.103, .792)], respectively. Moreover, plasmatic VEGF levels increased gradually along with the severity of ICAS ($P = .003$), and lower levels of ES ($P = .040$) or a higher VEGF/ES ratio ($P = .048$) were related to unfavorable short-term prognosis of ICAS. *Conclusion:* Lower VEGF levels are associated with the presence of symptomatic ICAS, but not with ECAS. Furthermore, the severity of ICAS is positively correlated with the levels of VEGF, and lower ES levels or a predominance of VEGF over ES are predictors of poor short-term prognosis of ICAS.
Key Words: Symptomatic intracranial atherosclerotic stenosis disease—symptomatic extracranial atherosclerotic stenosis disease—angiogenesis—vascular endothelial growth factor—endostatin—risk factors—short-term prognosis.

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Compliance with ethical standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

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Introduction

Ischemic stroke is one of the most common causes of mortality and disability worldwide.[1] The locations of vascular lesions have striking ethnic heterogeneity. Intracranial atherosclerosis disease (ICAD) is found commonly in Asian, African American, and Hispanic populations, whereas extracranial atherosclerosis disease is more prevalent in Caucasians.[2] Susceptible population, risk factors, plaque characteristics, stroke mechanisms, and prognosis are significantly different between intracranial atherosclerotic stenosis (ICAS) and extracranial atherosclerotic stenosis (ECAS) patients.[3-8] Circulating biomarkers may represent a powerful tool to assess the pathophysiology of diseases in vivo. Hence, finding out effective biomarkers to differentiate ICAS and ECAS is valuable.

Angiogenesis, which is induced by hypoxia and inflammation, could enhance oxygen to the occlusive tissue and facilitate the collateral circulation.[9,10] It is known that angiogenesis has a close relationship with atherosclerosis. The constitutions and characteristics of intracranial arteries are different from those of extracranial arteries such as the lack of vasa vasorum, a high antioxidant capacity, low inflammatory reaction, and protective effects of the cerebrospinal fluid.[11] Therefore, the angiogenesis involved in ICAS is probably different from that in ECAS.[11,12]

Angiogenesis is modulated by several pro- and antiangiogenic molecules.[13] Vascular endothelial growth factor (VEGF), a known proangiogenic factor, is a signaling peptide released by endothelial cells and smooth muscle cells and can promote vascular endothelial cell proliferation and angiogenesis.[14,15] Endostatin (ES), an important antiangiogenic factor, is a 20 kDa protein fragment derived from the collagen XVIII and can inhibit the proliferation and migration of endothelial cells, and then inhibit ischemia-induced neovascularization.[16,17] It also serves as a potent inhibitor of angiogenesis and tumor growth in vivo.[18] VEGF and ES play important roles in atherosclerosis and ischemia stroke process.[13,19] The importance of VEGF and ES in intracranial atherosclerosis has been previously addressed in several studies. For example, Massot et al found that patients with symptomatic ICAD have a lower concentration of fibroblast growth factor (FGF), VEGF, and platelet-derived growth factor-BB (PDGF-BB) than healthy controls.[20] Decreased levels of VEGF have been found in intracranial atherosclerotic disease and ES has been reported to be associated with a greater extent and risk of recurrence of symptomatic intracranial atherosclerosis in Spanish studies.[20,21] Lee et al found that increased serum level of VEGF might be correlated with degree of extracranial carotid artery stenosis in Korean population.[22] However, there has been no report on the comparison of pro- and antiangiogenic factors between different locations of cerebrovascular stenosis.

The main objective of the present study is to investigate whether there is a differential profile of vascular risk factors and angiogenesis-related biomarkers between extra- and intracranial atherosclerotic stenoses among patients with acute ischemic stroke in a Chinese Han population. So we performed the comparative studies of the 2 most typical pro- and antiangiogenic molecules (VEGF and ES) between ICAS and ECAS groups. In addition, the relationship between VEGF and ES and the severity or short-term prognosis of symptomatic intracranial stenosis was also assessed.

Patients and Methods

Subjects

We consecutively enrolled patients admitted to our hospital with acute (<7 days after onset) cerebral ischemic stroke, which was confirmed by computed tomography (CT) and/or magnetic resonance imaging (MRI) from August 2012 to March 2014. Data were collected through case report forms. Only those patients who met the following criteria were included in the present study: (1) age between 18 and 80 years; (2) having undergone the evaluation of cerebral vascular-like MRA/CTA/DSA/CE-MRA or transcranial Doppler (TCD) and/or carotid color duplex ultrasonography; and (3) having been classified into large-artery atherosclerosis (LAA) or small-artery occlusion (small-vessel occlusion, SVO) according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification.[23] The other 3 subtypes (cardioembolism, stroke of other determined etiology, stroke of undetermined etiology) were excluded.[23] Those patients who are non-Chinese as well as with serious infection, severe hepatic and renal dysfunction, malignant tumor, and autoimmune diseases were also excluded. Baseline data like age, sex, medical history, stroke risk factors, and physical examinations were also collected. All patients underwent comprehensive diagnostic workups including routine laboratory assessments, electrocardiography, echocardiography, and other evaluation when necessary. Short-term neurological outcome of patients was evaluated by a well-trained neurologist on the 14th day after stroke onset using the modified Rankin Scale (mRS) score. Favorable outcome was defined as mRS less than or equal to 2; unfavorable outcome was defined as mRS greater than or equal to 3 or death. The study was approved by the local ethics committee; a consent form was obtained from all the enrolled patients.

Imaging Assessment

All patients underwent conventional neuroimaging and vascular imaging test. Brain MRI and three-dimensional TOF-MRA (time-of-flight magnetic resonance angiography) on a 1.5 or 3.0 T magnetic resonance scanner were performed in most patients; CT and CTA (computed tomography angiography) were performed in MR-contraindicated or noncompliant patients. Intracranial