The Detrimental Effect of Aging on Leptomeningeal Collaterals in Ischemic Stroke

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Background: Aging is associated with decreased penumbral salvage in patients with ischemic stroke. Another critical factor that determines the fate of penumbra tissue is the degree of collateral circulation, which decreases significantly with aging in experimental models of stroke. In this study, we sought to identify whether these observations could be translated to humans and, therefore, analyzed the effect of patient age on extent of leptomeningeal collaterals in patients with ischemic stroke. *Methods:* Computed tomography angiography (CTA) source images were used to assess the degree of collateral circulation in a retrospective series of patients with proximal middle cerebral artery (MCA) occlusion. Bivariate and multivariate analyses were used to explore the relationship between patient age and degree of collateral circulation. *Results:* A total of 70 patients were included into the study. Older age ($P = .005$), history of hypertension ($P = .036$), higher admission National Institutes of Health Stroke Scale (NIHSS) scores ($P = .013$), and increased time to CTA ($P = .013$) were associated with inadequate collaterals in bivariate analyses. In multivariate analysis, older age ($P = .008$) and higher NIHSS scores ($P = .032$) remained as the only significant independent variables that were associated with inadequate collaterals. A 10-year increment in patient age increased the odds of inadequate collateral circulation by 1.87 (95% confidence interval: 1.18-2.97). *Conclusion:* Our findings show that there is a significant interplay between patient age and adequacy of leptomeningeal collateral circulation in patients with proximal MCA occlusion. The relationship could contribute to adverse tissue outcome and thereby to unfavorable clinical outcome observed in elderly patients with ischemic stroke. **Key Words:** Cerebral infarction—computed tomography scan—angiography—imaging—pial vessels—collateral circulation—aging.

Introduction

The leptomeningeal collateral network plays an important role in cerebral blood flow dynamics in the setting of acute ischemic stroke. The presence of adequate collaterals has been shown to be associated with improved tissue outcome,[1] better response to intravenous or intra-arterial thrombolysis,[2-4] lower risk of hemorrhagic transformation,[5] and favorable clinical outcome.[2,4,6] However, the extent of collateral circulation varies widely among individuals,[7] and there are no well-defined variables that might be used to predict the adequacy of collaterals.[8] The identification of factors that play a role in the collateral reserve following an acute vascular occlusion will not only be important in understanding the variability in cerebral hemodynamics in the acute stroke setting but also might prove to be useful in patient selection for collateral augmenting therapies.

Experimental studies have shown that aging causes a significant decrease in the number of leptomeningeal

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collaterals, together with increased tortuosity and vascular resistance in these vessels.[9,10] It is also well established from human studies that age has a detrimental effect on cerebrovascular reactivity.[11] More importantly, older age is associated with increased risk of conversion of penumbra tissue into infarction in patients with acute ischemic stroke,[12] which might theoretically be a reflection of impaired collateral reserve in elderly patients. In this study, we therefore analyzed whether patient age affected the extent of leptomeningeal collateral circulation in a cohort of patients presenting with middle cerebral artery (MCA) occlusion. Furthermore, we assessed the role of leukoaraiosis (LA) burden, a factor closely related to aging and impaired cerebrovascular reactivity, in this relationship.

Methods

Study Population

This study was a retrospective analysis of patients with a diagnosis of ischemic stroke secondary to M1 segment MCA occlusion, who were admitted to a tertiary care center over a period of 5 years. Patients were identified from a departmental database to which all patients with a diagnosis of stroke are consecutively entered. The analyses were restricted to patients who had computed tomography angiography (CTA) within 24 hours of symptom onset. The study was approved by the local institutional review board.

Data Collection

Clinical data (age, gender, stroke risk factors, admission National Institutes of Health Stroke Scale [NIHSS] score, statin use, stroke etiology, time from symptom onset to CTA and magnetic resonance imaging [MRI]) were collected for each patient through the departmental database and retrospective chart review. We classified stroke etiology using the Causative Classification of Stroke system.[13]

Image Acquisition and Analysis

CTA was performed by multidetector row scanners (SOMATOM Emotion Duo or Sensation 16; Siemens, Erlangen, Germany) using a helical scanning technique after a single bolus injection of 100-130 mL nonionic contrast into an antecubital vein at 3-4 mL/s with a dynamic contrast bolus detection technique used for timing of acquisition (CareBolus; Siemens Medical Systems, Erlangen, Germany). Acquisition parameters were as follows: SOMATOM Emotion Duo: foramen magnum to vertex, 130 kV, 50 mAs, slice thickness 2 mm, reconstruction increment .7 mm; Sensation 16: aortic arch to vertex, 120 kV, 100 mAs, slice width 1 mm, slice collimation .75 mm, reconstruction increment .7 mm. MRI was performed using 1.5-T scanners (Magnetom TIM; Siemens, and Intera, Achieva; Philips, Netherlands). Fluid attenuated inversion recovery (FLAIR) sequences that were used for determination of LA volume were obtained with the following acquisition parameters: repetition time 8000-9000 ms, echo time 90-100 ms, inversion time 2000-2100 ms, matrix 224 × 256, slice thickness 5 mm with 10% interslice distance, and field of view 220-240 mm.

An emergency department radiologist with extensive experience in acute stroke imaging (E.A.), blinded to clinical and MRI data, used CTA source images to assess the degree of collateral circulation in the sylvian fissure and leptomeningeal convexity, based on a previously validated scoring system.[14] Briefly, this scoring system grades collateral vessels on a scale from 1 to 5, with 1 signifying absent collaterals and 5 signifying exuberant collaterals. Patients with a collateral score of 3-5 both within the sylvian fissure and leptomeningeal convexity were considered to have adequate leptomeningeal collaterals. In addition to the assessment of collateral status in sylvian fissure and leptomeningeal convexity, CTA was used to determine the presence of significant stenosis (>50%) or occlusion within the extracranial ipsilateral internal carotid artery, extracranial contralateral internal carotid artery, and extracranial bilateral vertebral arteries. All CTA assessments were performed while being blind to the clinical and MRI data. A neuroradiologist (R.G.) blinded to clinical and CTA data calculated LA volume on FLAIR images using MRIcro software (University of Nottingham, Nottingham, UK) by a previously described semiautomated thresholding algorithm.[15,16] LA was defined as hyperintense lesions in the supratentorial white matter within the region extending from the lateral ventricular border to the corticomedullary junction and sparing the convolutional white matter, U-fibers, corpus callosum, internal capsule, and anterior commissure.[17,18] LA volume was measured only in the contralateral hemisphere as the boundary of LA could be not be reliably determined in the hemisphere subjected to acute ischemia. LA volume was normalized according to head size using midsagittal cross-sectional intracranial area.[16]

Statistical Analysis

All numerical variables are expressed as median (interquartile range [IQR]). Mann–Whitney *U* test and chi-square test were used to assess the differences among patients with adequate and inadequate collaterals. A logistic regression model was used to determine the independent predictors of adequate collaterals. Independent variables for this analysis were chosen from variables with a *P* value of less than .15 in bivariate analyses. A backward selection algorithm was performed to prevent overfitting. A 2-tailed *P* value of less than .05 was considered significant. All statistical analyses were performed using SPSS 16.0.

Results

We identified a total of 112 patients with proximal MCA occlusion during the study period. Forty-two patients had