High Extent of Intracranial Carotid Artery Calcification Is Associated with Downstream Microemboli in Stroke Patients

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Background: Intracranial arterial calcification (ICAC) is frequently detected on head computed tomography and has been found to be associated with ischemic stroke by recent clinical studies. *Aims:* Based on a hospital-based study, we aimed to compare the occurrence of cerebral microembolic signals (MES) among stroke patients with different degrees of ICAC, which may indicate the potential mechanisms linking ICAC and ischemic stroke in intracranial atherosclerosis patients. *Methods:* This is a post-hoc analysis of our previous clinical study in 2005-2007, recruiting consecutive ischemic stroke patients with middle cerebral artery territory infarctions and good temporal window for MES monitoring. The degrees of ICAC in the Circle of Willis, especially calcification in the ipsilateral intracranial internal carotid artery (iICA), were evaluated both qualitatively and quantitatively on unenhanced head computed tomography. *Results:* Among the 68 recruited patients, MES was detected in 26 patients (38.24%). The overall degree of ICAC in the Circle of Willis was similar between patients with and without MES. For calcification in ipsilateral iICA, the presence of MES was more frequent in the high extent group (widest arc of calcification ≥90°) than in the low extent group (54.2% versus 29.5%, $P = .046$). Logistic regression found that a high extent ipsilateral iICA calcification was an independent risk factor of MES (odds ratio: 3.134; 95% confidence interval, 1.029-9.543; $P = .044$). *Conclusions:* MES is frequently detected in patients with a high extent of ipsilateral iICA calcification, which suggests that a high extent of iICA calcification indicates artery vulnerability and accounts for the occurrence of microemboli in the corresponding artery. **Key Words:** Intracranial arterial calcification—microembolic signals—atherosclerosis—stroke.

Atherosclerosis causes clinical events through luminal narrowing or by precipitating thrombi and emboli that obstruct blood flow to the brain (ischemic stroke) or heart (coronary heart disease).[1] Intracranial atherosclerosis (ICAS) is a well-recognized cause of ischemic stroke. Intracranial arterial calcification (ICAC), which is an important indicator of ICAS, was first observed by radiographic pathology in early 1960s.[2] Later studies found 89% of Chinese patients and 82% Dutch patients who are >55 years have ICAC on conventional head computed tomography (CT).[3,4] Given the systemic nature of atherosclerosis, the confirmation of coronary calcium score as a predictor of future cardiac events has spurred researchers' interests on ICAC. Recent clinical studies have demonstrated the association between ICAC and ischemic stroke.[5,6] However, the

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underlying pathophysiological mechanism linking ICAC and ischemic stroke is yet unclear.

According to the literature, there are four main hypothesized mechanisms of ICAS-related stroke: artery-to-artery embolism, local branch occlusion, in situ thrombo-occlusion, and hemodynamic impairment.[7] Artery-to-artery embolism is the most common mechanism and is found in 46%~51% of ICAS-related stroke patients.[8,9] For middle cerebral artery (MCA) territory infarctions with different etiologic classifications, embolic occlusion of MCA either from the heart or the atherosclerotic internal carotid artery is considered to be the main cause. Atherosclerotic emboli may derive from both portion of thrombus broken up by forceful blood flow and atherosclerotic debris from ulceration of the surface of the plaque.[7,10] Cerebral microembolic signals (MES) detected by transcranial Doppler (TCD) monitoring is the direct evidence of artery-to-artery embolism. Being frequently found in patients with large artery diseases, MES confers increased risk of transient ischemic attack, stroke, and recurrent stroke.[11-13]

In this study, we aimed to explore the relationship between severity of ICAC and occurrence of MES in symptomatic MCA, which may help better understand the stroke mechanism in ICAS patients, and highlight the role of ICAC in predicting future stroke risk.

Materials and Methods

Subjects

This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. The patient series came from previous potential candidates of the CLAIR study,[14] in which a total of 200 consecutive ICAS-related ischemic stroke patients admitted to the Acute Stroke Unit of Prince of Wales Hospital in 2005-2007 with symptom onset within 7 days and good temporal window were recruited and screened by MES monitoring. Ischemic stroke was diagnosed according to the definition of World Health Organization. Cerebral large artery occlusive disease (moderate artery stenosis or ≥50% diameter reduction) was determined by TCD, magnetic resonance angiography, or CT angiography. Being interested in the effect of ICAC on embolic stroke, in the present study, only patients with clinical features compatible with stroke in the stenotic MCA were recruited. We excluded 131 patients whose culprit artery was not ipsilateral MCA or who did not have CT or magnetic resonance imaging evidence that confirmed stenotic MCA territory infarctions. One more patient was excluded due to losing the CT brain source images, so a total of 68 patients were included in this study.

Age, gender, smoking habit, and medical history (including hypertension, diabetes, hyperlipidemia, ischemic heart disease, and atrial fibrillation) were recorded. The National Institutes of Health Stroke Scale score were used to evaluate the severity of index stroke.

MES Detection

MES was detected according to the method described previously.[13,14] Briefly, TCD was performed within 7 days from symptom onset using TC 2020 machine (Nicolet-EME, Kleinostheim, Germany). A 30-minute recording was taken of the ipsilateral MCA distal to any symptomatic MCA or carotid artery stenosis. The procedure followed the international consensus on MES monitoring. The data were analyzed by an experienced observer, who was blinded to the clinical data. The presence of MES was identified by the following criteria: typical visible and audible (click, chirp, and whistle), short-duration, high-intensity signal within the Doppler flow spectrum, with its occurrence at random in the cardiac cycle.[15]

Calcification Assessment

Image Acquisition

The conventional unenhanced head CT was performed with a multi-detector CT system (General Electric, WI, USA), with the following parameters: 140 kVp, field of view of head, 170 mAs, 2 seconds per rotation, detector combination 16 × .625 mm, axial mode. The whole brain was covered from the skull base to the vertex.

On the .625 mm axial CT images (bone window), ICAC was defined as hyperdense foci with attenuation number more than 130. An experienced neurologist, who was blinded to all the clinical data, evaluated the degree of ICAC. The involvements of arterial calcification were assessed in the bilateral intracranial internal carotid artery (iICA), anterior cerebral arteries, MCAs, posterior cerebral arteries, basilar artery, and intracranial vertebral arteries. All CT images were retrospectively analyzed in 2015.

Visual Grading

The extent and thickness of calcification in the intracranial arteries were scored on a 5-point scale (0-4) suggested by Babiarz et al[16] (Table 1). To calculate the total score of ICAC within the brain vasculature, the artery with the highest score was selected. For ipsilateral iICA, the extent score was divided into high extent (scoring 3-4, widest arc of calcification ≥90°) and low extent (scoring 0-2, widest arc of calcification <90°) groups, and the thickness score was divided into high thickness (scoring 3-4, >2 mm thick) and low thickness (scoring 0-2, ≤2 mm thick) groups for comparisons.

Quantitative Assessment

The ICAC Agatston score and calcium volume were analyzed using a semi-automatic system with a custom-made program. All CT source images were first conversed to three-dimensional images by the MATLAB software (R2015a, MathWorks Corporation, Natick, MA, USA). ICAC was subsequently semi-automatically segmented by