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Clinical Study

Acute stroke with major intracranial vessel occlusion: Characteristics of cardioembolism and atherosclerosis-related *in situ* stenosis/occlusion

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ABSTRACT

Acute ischemic stroke with major intracranial vessel occlusion is commonly due to cardioembolic or atherosclerosis-related *in situ* stenosis/occlusion, and immediate identification of these subtypes is important to establish the optimal treatment strategy. The aim of this study was to clarify the differences in clinical presentation, radiological findings, neurological temporal courses, and outcomes between these etiologies, which have not been fully evaluated. Consecutive emergency patients with acute ischemic stroke were retrospectively reviewed. Among them, patients with stroke with major intracranial vessel occlusion were analyzed with a focus on clinical and radiological findings, and a comparison was performed for those with cardioembolic or atherosclerosis-related *in situ* stenosis/occlusion. Of 1053 patients, 80 had stroke with acute major intracranial vessel occlusion (45 with cardioembolic and 35 with atherosclerosis-related *in situ* stenosis/occlusion). Interestingly, the susceptibility vessel sign (SVS) on T2-weighted MR angiography was more frequently detected in cardioembolic stroke (80.0%) than in atherosclerosis (*in situ* stenosis: 5.9%, chronic occlusion: 14.3%). Moreover, the proximal intra-arterial signal (IAS) on arterial spin labeling MRI and the distal IAS on fluid attenuated inversion recovery MRI was less frequently detected in chronic occlusion (27.3% and 50.0%, respectively) than in acute occlusion due to cardioembolic or *in situ* stenosis. Multivariate regression analysis showed that the SVS was significantly related to cardioembolism (adjusted odds ratio (OR): 21.68, $P = 0.004$). Clinical characteristics of acute stroke with major intracranial vessel occlusion differ depending on the etiology. The SVS and proximal/distal IAS on MRI are useful to distinguish between cardioembolic and atherosclerotic-related *in situ* stenosis/occlusion.

1. Introduction

It is well known that immediate reperfusion is a strong indicator of stroke outcome in patients with acute major intracranial vessel occlusion, and many clinical trials have debated the efficacy of endovascular mechanical reperfusion over intravenous recombinant tissue plasminogen activator (t-PA) [1]. To achieve a good clinical outcome with these reperfusion therapies, identification of the stroke subtype is very important, including stroke associated with cardioembolism, atherosclerotic *in situ* stenosis, and chronic occlusion; additionally, the salvageable brain area should be evaluated using CT or MR perfusion.

Recent advances in MR techniques have enabled direct imaging of the thrombus, and the susceptibility vessel sign (SVS) on T2-weighted MR imaging is reportedly related to the presence of a deoxyhemoglobin-rich thrombus in acute vessel occlusion [2–4]. The SVS is an independent factor associated with the absence of early recanalization within 1 h after t-PA administration [5]. On the other hand, an intra-arterial high-intensity signal (IAS) on arterial spin labeling (ASL) is also reportedly useful for identification of the presence of acute vessel occlusion showing stagnant flow in front of occlusion sites [6,7]. Moreover, the presence of a distal IAS on fluid-attenuated inversion recovery (FLAIR) images was found to be a marker of collateral circulation and associated with large diffusion-perfusion mismatch [8,9]. Each characteristic radiological sign could represent the clot composition or intravascular hemodynamic status around the occlusion vessels, but no reports have investigated the etiology of stroke accompanying

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major intracranial vessel occlusion with a combination of these radiological signs.

In this study, we aimed to clarify the characteristics of stroke due to cardioembolic or atherosclerosis-related *in situ* stenosis/occlusion by focusing on the SVS, proximal and distal IAS, clinical presentation, neurological temporal course, and outcome.

2. Methods

2.1. Study population

From April 2011 to April 2014, consecutive emergency patients with acute ischemic stroke were retrospectively reviewed at Nagasaki University Hospital. Among them, patients with stroke accompanying major intracranial vessel occlusion who had adequate initial and follow-up examination data were analyzed, focusing on the clinical and radiological differences between cardioembolic and atherosclerosis-related *in situ* stenosis/occlusion. The selection criteria for this study were as follows: (1) patients with acute symptomatic stroke with major intracranial vessel occlusion (internal carotid artery, middle cerebral artery: proximal and distal M1 segments and basilar artery), (2) patients who underwent MR imaging including diffusion weighted imaging (DWI), T2-weighted MR angiography (SWAN), ASL, FLAIR, and MR angiography on arrival, 24 h after onset, and 14 days after onset, and (3) adequate follow-up examination data were obtained until day 90. Cardiac function-related markers and coagulation/fibrinolysis-related markers were also evaluated with blood biochemistry testing at onset. The temporal course of neurological severity was assessed with the National Institute of Health (NIH) stroke scale, and the final outcome was assessed using the modified Rankin Scale (mRS) and Barthel Index (BI) at day 90.

Cardioembolic stroke was defined as the presence of atrial fibrillation, myocardial infarction in the past 6 months, or a high-risk source of embolism identified on echocardiogram according to Trial of Org 10172 in Acute Stroke Treatment criteria [10]. Atherosclerosis-related *in situ* stenosis and chronic occlusion was diagnosed based on findings of prior MR angiography, postoperative digital subtraction angiography/MR angiography, or follow-up MR angiography >14 days from onset. Patients with arterial occlusion due to intracranial dissection were excluded from this study.

2.2. MR imaging parameters

All patients with acute stroke underwent MR imaging analysis unless they had a contraindication for MR imaging. The MR imaging protocol was same regardless of the stroke subtype or presence of vessel occlusion. MR imaging was performed with a 1.5-Tesla unit (Signa HDxt; GE Healthcare, Milwaukee, WI, USA) using an eight-channel phased-array coil. The acute stroke MR protocol, which was performed during a single session within 20 min, comprised DWI, FLAIR, 3D time-of-flight MR angiography, 3D SWAN, and 3D ASL.

Axial DWI was obtained with the following parameters: repetition time (TR)/echo time (TE), 10000/82 ms; 3 motion-probing gradient directions with a b value of 1000 s/mm^2; matrix size, 128 × 192; field of view (FOV), 27 cm; and slice thickness, 5 mm with a 1-mm gap. The axial FLAIR parameters were as follows: TR/TE: 8000/112 ms; TI: 2000 ms; matrix size, 256 × 192; FOV, 22 cm; and slice thickness, 5 mm with a 1-mm gap. 3D TOF MRA was obtained in an axial plane with the following parameters: TR/TE, 28/3.3 ms; flip angle (FA), 20°; FOV, 19 cm; matrix size, 192 × 320; and slice thickness, 1.4 mm.

SWAN is a T2-weighted 3D-gradient echo pulse sequence that acquires multiple echoes during one TR period at different time points. The echoes are centered equidistantly in time on an effective TE to achieve a series of images with different TEs. From this series of images with different T2 weightings, a collapsed image is calculated by building the sum of the squares of the different echoes. The axial SWAN parameters were as follows: TR/effective TE, 63.8/49.8 ms; FA, 15°; matrix size, 192 × 384; FOV, 22 cm; slice thickness 3 mm; NEX, 0.7.

3D ASL was performed by use of a pseudo continuous labeling period of 1500 ms, followed by a 2500 ms post-label delay. Whole axial brain images were obtained with a 3D background-suppressed fast spin-echo (FSE) stack-of-spirals method, with a TR/TE of approximately 5281/13.8 ms; FOV, 24 × 24 cm; and NEX, 4. Multi-arm spiral imaging was used, with 4 arms and 1024 points acquired on each arm, yielding an in-plane and through-plane spatial resolution of 3.5 and 6.0 mm, respectively.

2.3. Evaluation of SVS, proximal IAS, and distal IAS

The SVS was defined as a low intensity signal spot with a blooming effect on SWAN in the occlusion site, and the proximal IAS was defined as a high intensity signal spot in and around the occlusion site. The distal IAS was also defined as a high intensity signal in the cortical vessels distal to the occlusion point. These signs were defined and evaluated according to previous reports [2,6,9].

2.4. Image analyses

MR images were separately analyzed by two experienced readers (N.H. and M.M.), and decisions were made by consensus. Both readers were blinded to the radiological and clinical characteristics. To establish the reproducibility of our qualitative assessment, two different readers (N.H. and Y.T.) and one reader (N.H.) determined the interobserver and intraobserver agreement, respectively, with application of Cohen's kappa at an interval of >7 days. Cohen's kappa was evaluated using an established grading of agreement: 0.00 (no agreement), 0.00–0.20 (poor), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1.00 (nearly perfect).

2.5. Statistical analysis

Data were tested for normality of distribution and equal standard deviations using GraphPad InStat version 3.10 (GraphPad Software, La Jolla, CA, USA) to determine whether parametric or nonparametric assumptions should be used for each statistical method. Comparisons between groups were performed using the Mann–Whitney test for continuous variables and the chi-squared test for categorical variables. Multivariate logistic regression analysis was performed to identify factors associated with cardioembolic stroke or chronic occlusion. Unless stated otherwise, differences were considered statistically significant at $p < 0.05$.

3. Results

Of 1053 patients, the percentage of cardioembolism and atherosclerosis were 42.3% (445 patients) and 23.0% (242 patients), respectively. Among them, 48 patients with cardioembolism and 35 patients with atherosclerosis had large vessel occlusion. Three patients with cardioembolism were excluded because of poor examination due to restlessness. The patients' characteristics are shown in Table 1. Of 80 patients, 45 exhibited cardioembolism and 35 exhibited atherosclerosis-related *in situ* stenosis/occlusion