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Original Article

Prediction of hemorrhagic transformation after acute thrombolysis following major artery occlusion using relative ADC ratio: A retrospective study

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ABSTRACT

Background. – The relative apparent diffusion coefficient (ADC) ratio can be used to evaluate the extent of ischemia. We investigated the risk factors for, and correlation between, relative ADC ratio and hemorrhagic transformation (HT) after thrombolysis.
Methods. – This single-center, retrospective study involved 105 patients with acute occlusion of the anterior circulation. Relative ADC ratio was calculated as the ratio of ADC pixel values, within the affected territory to ADC pixel values in the contralateral normal region. HT was determined by computed tomography and T2* weighted magnetic resonance imaging after endovascular revascularization.
Results. – Data for 80 of the 105 patients were analyzed. Comparing the number of patients between the HT group ($n = 25$) and the non-HT group ($n = 55$), a significant difference was noted in tissue plasminogen activator (tPA) use ($P = 0.028$), time from onset to reperfusion ≥ 380 min ($P < 0.001$), fluid-attenuated inversion recovery (FLAIR) hyperintensity ($P = 0.009$), and relative ADC ratio < 0.650 ($P < 0.001$). Multivariable logistic regression analysis identified relative ADC ratio < 0.650 as the only independent predictor of HT (odds ratio 7.79; 95% confidence interval 2.22–27.3; $P = 0.001$). Twenty-nine patients (including 20 in the HT group) had a relative ADC ratio < 0.650. Multivariable logistic regression analysis identified use of tPA as the only independent predictor of HT (odds ratio 13.8; 95% confidence interval 1.35–125.5; $P = 0.010$).
Conclusions. – Relative ADC ratio < 0.650 with use of tPA may be important for predicting HT.

Introduction

Hemorrhagic transformation (HT) after thrombolysis increases the morbidity and mortality of ischemic stroke [1]. A recent study showed that anatomical and physiological disruption due to extravasation of blood is highly dependent on the degree of ischemia before treatment [2]. In a previous study, we demonstrated that hemorrhagic transformation was observed in regions where relative ADC ratio was strongly decreased locally on pretreatment magnetic resonance imaging (MRI) [3].

Using MRI, both fluid-attenuated inversion recovery (FLAIR) hyperintensity within the area of diffusion restriction and the ratio of decrease in the apparent diffusion coefficient (ADC) sequence can be used to evaluate the degree of ischemia. FLAIR hyperintensity may be the result of net increased water content in pathological tissue following severe ischemia, cytotoxic edema, or increased blood-brain barrier (BBB) permeability [4,5]. Clinical research in 109 patients showed that early development of FLAIR hyperintensity within the area of diffusion restriction is associated with increased risk of HT, after thrombolysis in patients treated with tissue plasminogen activator (tPA) < 4.5 h after onset [6]. Conversely, Sakoh et al. reported that a decrease in ADC (< 75% of the control) correlated significantly with a reduction in the cerebral metabolic rate of oxygen (50% of the control) [7]. Other studies have demonstrated that the relative ADC ratio might be correlated with bioenergetic compromise of ischemic tissue [8–13]. However,

Abbreviations: ADC, apparent diffusion coefficient; BBB, blood-brain barrier; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; HT, hemorrhagic transformation; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hematoma; TICI, thrombolysis in cerebral infarction; tPA, tissue plasminogen activator.

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the correlation between the relative ADC ratio and HT after thrombolysis remains unclear.

Previous studies have identified some risk factors for HT after thrombolysis, including age, stroke severity, smoking, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, past history of stroke, serum glucose levels, lesion volume on diffusion-weighted imaging (DWI), use of tPA, and age-related white matter changes on MRI [14–18]. In this study, we investigated these factors and assessed whether FLAIR hyperintensity within the area of diffusion restriction or the relative ADC ratio was more useful for predicting HT after thrombolysis.

Materials and Methods

This single-center retrospective study was reviewed and approved by the Institutional Review Board of our hospital (No. 1515) and adhered to the principles of the Declaration of Helsinki. Consecutive patients with a diagnosis of acute stroke between April 2012 and July 2016 were enrolled.

We analyzed 105 patients with a known time of symptom onset within 6 h of presentation who presented with acute occlusion of the anterior circulation (internal carotid artery or middle cerebral artery [MCA]; M1 + M2) confirmed on MRI. All patients underwent imaging analysis using computed tomography (CT), followed by MRI examination (DWI, ADC, FLAIR, and magnetic resonance angiography [MRA]) immediately at the time of hospitalization. CT findings were used to exclude patients with hemorrhage or parenchymal ischemic changes exceeding one-third of the MCA territory before administration of acute fibrinolytic therapies. The patients underwent thrombolysis with 0.6 mg/kg body weight tPA consistent with the National Institute of Neurological Disorders and Stroke tPA Stroke Study Group protocol [19]. All patients underwent endovascular revascularization for large vessel occlusion (including patients in whom tPA therapy had failed and those who had received off-label thrombolysis). Patients in whom post-operative angiography revealed recanalization to thrombolysis in cerebral infarction (TICI) status 2a, 2b, or 3 were included in the study. Patients who received no treatment or tPA therapy alone and those in whom recanalization status was TICI 0 or 1 were excluded.

MRI was performed by using a 1.5-T scanner (Achieva, Philips, Amsterdam, the Netherlands). The minimum MRI protocol performed at the time of hospitalization and again within 24 h after treatment included the following sequences: DWI and ADC (spin echo, b-values = 1000 s/mm^2, TE = 87 ms, TR = 2550 ms, field of view [FOV] = 230 mm, matrix = 256 × 128, 6.0-mm section thickness with a 1.0 mm intersection gap); ADC (spin echo, TE = 87 ms, TR = 2550 ms, FOV = 230 mm, matrix = 256 × 128, 6.0 mm section thickness with a 1.0 mm intersection gap); FLAIR (turbo spin echo, TE = 120 ms, TR = 6000 ms, FOV = 230 mm, matrix = 256 × 128, TI = 2000 ms, 6.0 mm section thickness with 1.0 mm intersection gap); T2* (fast field echo, TE = 18 ms, TR = 636 ms, FOV = 230 mm, matrix = 256 × 128, 6.0 mm section thickness with a 1.0 mm intersection gap); and time-of-flight MRA (fast field echo, TE = 6.9 ms, TR = 20 ms, FOV = 200 mm, matrix = 512 × 204, 0.65 mm section thickness with a 0.72 mm intersection gap).

The images were processed using a Fujifilm Medical Systems workstation with Synapse Enterprise-PACS software. The region of interest (ROI) was analyzed using standard planimetric techniques by an observer with knowledge of the side of the infarct. The average pixel values of the lesions were calculated. Relative ADC ratio was calculated as the ratio of the ADC pixel values within the affected territory to the ADC pixel values in the corresponding contralateral normal brain region. An upper threshold for the average rate of ADC values per pixel in the ROI was applied to eliminate the effect of the cerebrospinal fluid mask, so the ROIs in the affected and unaffected hemispheres do not have an identical shape (Fig. 1). Acute lesions of ADC sequences were manually outlined based on the DWI. When the boundary between the lesion and normal tissue was unclear, we delineated it more accurately using enlarged images. Three-dimensional volume data for the acute DWI lesions were retrospectively measured in each 6 mm slice DWI data combination (Fig. 2).

HT was determined by CT scan and T2* weighted MRI within 24 h after treatment. Hemorrhagic infarction was defined as petechial HT without mass effect and parenchymal hematoma (PH) as HT with mass effect based on the criteria recommended by Fiorelli et al. [20]. Along with FLAIR hyperintensity and the relative ADC ratio, we evaluated the time interval from onset to first MRI, time from onset to reperfusion, and previously established risk factors for stroke, that is, age, stroke severity (National Institutes of Health Stroke Scale, NIHSS), smoking, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, past history of stroke, serum glucose levels, DWI lesion volume, tPA use, and age-related white matter changes on MRI. When we recognized a significant difference for a parameter, we selected the optimal cut-off point between the HT and non-HT groups using receiver-operating characteristic

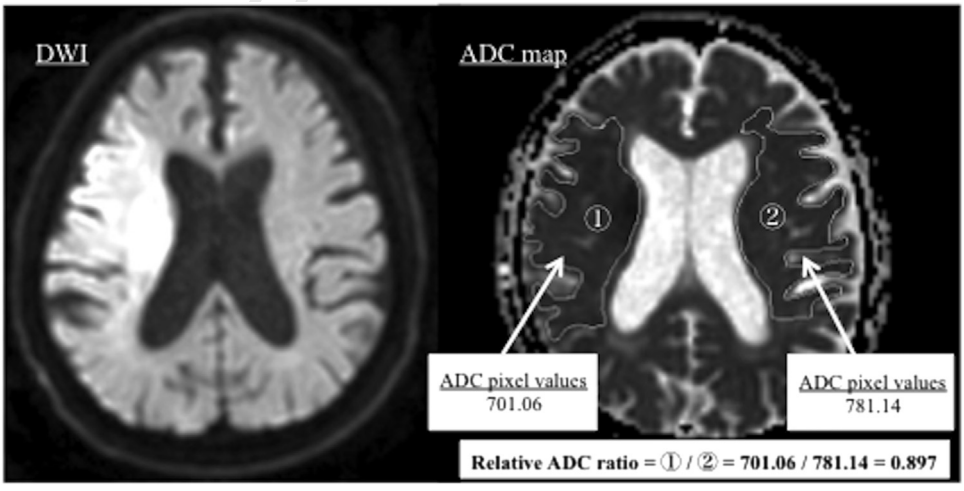

Fig. 1. Example of the ratio of apparent diffusion coefficient (ADC) decrease as seen on MRI. Acute lesions of ADC sequences are manually outlined based on the diffusion-weighted imaging (DWI). DWI and ADC are shown on the left and right respectively. The relative ADC ratio was calculated as the ratio of the ADC pixel values within the affected territory (1) to those in the contralateral normal brain regions (2).

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