Original Article

Apparent diffusion coefficient value for prediction of hemorrhagic transformation in acute ischemic infarction

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Received February 6, 2017; Accepted November 27, 2017; Epub January 15, 2018; Published January 30, 2018

Abstract: Objective: We investigated the role of apparent diffusion coefficient (ADC) values in assessing the risk of hemorrhagic transformation in acute cerebral infarcts. Materials and methods: Fifty-eight patients with acute ischemic infarction undergoing magnetic resonance (MR) examinations, including diffusion-weighted imaging (DWI) and susceptibility weighted imaging (SWI), were included. Repeat MR examinations were performed within two weeks after admission. Patients were divided into hemorrhagic transformation (HT) group and non-HT group. The minimum and mean ADC values of the cerebral infarct areas were measured on the initial DWI. Between-group differences in ADC values were assessed using two-sample t-test. Results: Twenty-eight (48.3%) patients had developed HT, while no evidence of HT was observed in 30 (51.7%) patients. Patients with HT had lower minimum and mean ADC values (P < 0.05 vs. non-HT group). The optimal cut-off level of minimum ADC value for predicting HT was 450 × 10^-6 mm^2/s, and that of mean ADC value was 500 × 10^-6 mm^2/s. Conclusion: Change in signal intensity on the ADC map and quantitative analysis of the ADC values may help predict hemorrhagic transformation in patients with early ischemic infarction.

Keywords: Cerebral infarction, hemorrhagic transformation, diffusion-weighted imaging, apparent diffusion coefficient

Introduction

Ischemic cerebral infarction (also referred to as ischemic stroke) accounts for approximately 60%-80% of all cerebrovascular events [1]. Ischemic stroke is more common than hemorrhagic stroke and is a major contributor to mortality and long-term disability throughout the world [1, 2].

Hemorrhagic transformation (HT), which refers to secondary bleeding into the ischemic cerebral area after stroke, is a serious complication [2, 3]. It may occur following anticoagulant and thrombolytic therapy as well [4]. HT is believed to be a consequence of ischemic injury to brain microvasculature. This complication occurs in 8.5%-30% of all patients with ischemic stroke [5]. Severe HT can worsen the patient's condition and may even be fatal. Since the treatment and prognosis of HT are distinct from those of ischemic cerebral infarction, early prediction and identification of HT is a clinical imperative. Several clinical parameters and blood biomarkers associated with an increased risk of HT have recently been reported [3, 6-8].

Magnetic resonance imaging (MRI) is widely used for the diagnosis and evaluation of cerebral ischemia. Traditional T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) do not adequately delineate the acute lesions in the initial hours after ischemic stroke; moreover, these are not useful to assess the risk of HT. Diffusion-weighted imaging (DWI) is sensitive to the changes in the diffusion of water molecules associated with cytotoxic edema; the movement of these molecules is liable to be restricted in ischemic areas of the brain. The degree of this restriction can be quantified by measuring apparent diffusion coefficient (ADC) value [9-11]. DWI has been shown to be effec-
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Table 1. Magnetic resonance scanning parameters

<table>
<thead>
<tr>
<th>Magnetic resonance sequence</th>
<th>Repetition time/echo time</th>
<th>Section thickness/intersection gap (cm)</th>
<th>Bandwidth (Hz)</th>
<th>NEX</th>
<th>Matrix</th>
<th>FOV</th>
<th>Scan time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1WI</td>
<td>1500/24</td>
<td>6/2</td>
<td>27.78</td>
<td>2</td>
<td>320 x 224</td>
<td>24 x 24</td>
<td>2:17</td>
</tr>
<tr>
<td>T2WI</td>
<td>4600/121</td>
<td>6/2</td>
<td>31</td>
<td>1.5</td>
<td>448 x 448</td>
<td>24 x 24</td>
<td>1:55</td>
</tr>
<tr>
<td>DWI</td>
<td>6000/93.3</td>
<td>6/2</td>
<td>62.5</td>
<td>2</td>
<td>128 x 128</td>
<td>24 x 24</td>
<td>0:48</td>
</tr>
<tr>
<td>SWI</td>
<td>Min/54.1</td>
<td>2/0</td>
<td>41.67</td>
<td>0.69</td>
<td>448 x 320</td>
<td>24 x 24</td>
<td>4:00</td>
</tr>
</tbody>
</table>

NEX, number excitations; FOV, field of view; T1WI, T1 weighted image; T2WI, T2 weighted image; DWI, diffusion weighted imaging; SWI, susceptibility weighting imaging; Min, minimum.

Materials and methods

Subjects

This prospective study was approved by the local ethics committee. In this study, we enrolled 58 patients with ischemic cerebral infarction, who presented within 3 days from the onset of ischemia. Of these, 11 patients had presented ≤ 6 hours since the onset of acute ischemic stroke. Written informed consent was obtained from all individual participants and/or their relatives.

The inclusion criteria were: (1) confirmed diagnosis of acute ischemic cerebral infarction; and (2) availability of complete clinical and radiological data. Exclusion criteria included: (1) findings suggestive of HT on the initial MRI; and (2) critically ill patients, such as those with unstable blood pressure or coagulation disorders.

The diagnosis of HT was based on the following two criteria: (1) no hemorrhagic focus detected on the initial susceptibility weighted imaging (SWI); (2) hypointense cerebral infarcts detected on follow-up SWI. Patients were divided into two groups (HT group and non-HT group) according to the presence or absence of HT.

Neuroimaging examination

MRI scan was conducted on a 1.5 T scanner (Signa HD; GE Medical Systems, Milwaukee, Wisconsin).
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The imaging protocol included T1WI, T2WI, DWI, and SWI sequences (all axial scans). MRI examination was performed on admission and two weeks thereafter. The imaging parameters are presented in Table 1. DWI was acquired with a diffusion sensitizing gradient ($b$ values) of 0 and 1000 s/mm$^2$. The imaging parameters are presented in Table 1. DWI was acquired with a diffusion sensitizing gradient ($b$ values) of 0 and 1000 s/mm$^2$.

Data processing and analysis

All DWI images were processed with the specialized software, Functool of GE ADW 4.2 workshop. ADC analysis was performed on axial images, and the following sections were selected for measurement of ADC values. For evaluation on the initial MRI, in the HT group, we chose the section which corresponded with the follow-up MRI section that showed the largest area of the hemorrhagic lesion; in the non-HT group, we selected the section with the largest area of the infarct. The lateral cerebral ventricle was manually excluded to minimize CSF contamination. Regions of interest (ROIs) were drawn on the T2W images, and automatically transferred onto the corresponding ADC maps. Within each ROI, ADC values were determined on a pixel-by-pixel basis. The ADC values in the center of the infarct and at the four edges (top, bottom, left, and right) were measured, and the mean ADC value was calculated.

The SWI data was processed via rebuilding the minimum intensity projection. HT was defined as appearance of new hypointense lesions in the infarcts on follow-up scans.

Statistical analysis

Statistical analysis was performed using SAS software (version 9.4, SAS Institute, Cary, North Carolina). Two-sample t-test was used to compare the continuous variables; Chi-squared or Fisher exact test was used to compare the categorical variables. Student t test was used to compare the distribution of minimum and mean ADC values of the initial scans between the HT and the non-HT groups. Receiver operating characteristic (ROC) curve analysis was performed to assess the potential correlation of minimum and mean ADC values with the risk of HT. Log-binomial regression was used to estimate the relative risk of dichotomized minimum ADC and mean ADC values (cut-off values were set as $450 \times 10^{-6}$ mm$^2$/s and $500 \times 10^{-6}$ mm$^2$/s, respectively) on HT. A two-tailed $P$ value < 0.05 was considered indicative of a statistically significant difference.

Results

Clinical characteristics and HT analysis

There were 40 men and 18 women (age range, 35-89 years). The presenting clinical symptoms included dizziness, weakness of limbs, and
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slurring of speech. There was no evidence of HT (Figure 1) in 30 patients, out of which 6 were admitted within 6 hours from the onset of ischemia. On follow-up radiological examination, 28 patients were found to have developed HT (Figures 2 and 3); five of these were admitted within 6 hours from the onset of ischemia.

No significant between-group differences were observed with respect to general characteristics (Table 2).

**DWI analysis: the minimum and mean ADC values**

In the HT group, the minimum ADC values ranged between $250 \times 10^{-6}$ mm$^2$/s and $470 \times 10^{-6}$ mm$^2$/s, while the mean ADC values ranged between $350 \times 10^{-6}$ mm$^2$/s and $530 \times 10^{-6}$ mm$^2$/s. In the non-HT group, the minimum ADC values ranged between $390 \times 10^{-6}$ mm$^2$/s and $740 \times 10^{-6}$ mm$^2$/s, while the mean ADC values ranged between $460 \times 10^{-6}$ mm$^2$/s and $790 \times 10^{-6}$ mm$^2$/s (Figures 4 and 5). The minimum and mean ADC values in patients with HT were significantly lower than those in the non-HT group (two-sample t-test; $P < 0.05$) (Table 3).

**ROC analysis; Optimal cut-off level of minimum ADC value and mean ADC value**

ROC analysis revealed a high sensitivity and specificity of both minimum and mean ADC values in predicting HT after ischemic cerebral infarction. Area under the curve for minimum and mean ADC was 97.3% (95% Confidence Interval [CI], 93.6%-100%) and 98.1% (95% CI, 94.7%-100%), respectively.

A cut-off value of $450 \times 10^{-6}$ mm$^2$/s for minimum ADC value was associated with 85.7% (95% CI, 67.3%-96.0%) sensitivity and 93.3% (95% CI, 77.9%-99.2%) specificity. A cut-off value of $500 \times 10^{-6}$ mm$^2$/s for mean ADC value was associated with a sensitivity and specificity of 87.9% (95% CI, 74.5%-97.8%) and 95.6% (95% CI, 78.4%-99.5%), respectively (Figures 6 and 7).

**Table 2. Demographic and clinical characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HT group</th>
<th>Non-HT group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean ± SD)</td>
<td>63.8 ± 10.2</td>
<td>65.7 ± 9.8</td>
<td>0.459</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>19 (67.9%)</td>
<td>21 (70.0%)</td>
<td>0.860</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>23 (82.1%)</td>
<td>24 (80.0%)</td>
<td>0.835</td>
</tr>
<tr>
<td>Diabetes [n (%)]</td>
<td>21 (75.0%)</td>
<td>23 (76.7%)</td>
<td>0.882</td>
</tr>
<tr>
<td>Smoking [n (%)]</td>
<td>14 (50.0%)</td>
<td>11 (36.7%)</td>
<td>0.305</td>
</tr>
<tr>
<td>Alcohol use [n (%)]</td>
<td>11 (39.3%)</td>
<td>7 (23.3%)</td>
<td>0.189</td>
</tr>
</tbody>
</table>

HT, hemorrhagic transformation; SD, standard deviation.
Discussion

Pathogenesis and diagnosis

The pathogenesis of HT after acute ischemic stroke is not completely understood. The main hypotheses include: (1) increased vascular permeability following ischemic injury; (2) dislodgement of emboli and recanalization of occluded vessels; (3) high permeability of newly formed microvasculature; and (4) reperfusion injury to small vessels, damage to blood brain barrier, and increased microvascular permeability after subsidence of ischemic edema [13, 14]. All these factors may contribute to bleeding.

DWI has been widely used as a gold standard for diagnosis of ischemic stroke. DWI is more sensitive than ordinary T2-weighted imaging for detection of ischemia within several hours of
The primary event [9-11]. Acute cerebral infarction is associated with decrease in ADC values, which is attributable to the early pathophysiological changes including energy failure, microcirculation disturbance, tissue acidosis and cytotoxic edema [15]. In the early phase of ischemia, cerebral hypoxia and metabolic derangement may cause swelling of neuronal cells, narrowing of extracellular space, and restricted diffusion of water molecules outside of cellular boundaries/membranes. Reduced overall diffusion level in ischemic tissues manifests as decreased ADC values and hyperintensity on DWI. However, DWI is not able to reflect HT in the early stages. SWI is considered as an effective diagnostic modality for identification of HT owing to its exquisite sensitivity to venous blood, hemorrhage and blood degradation products. SWI is known to be the most sensitive MR sequence to detect different types of intracranial hemorrhage including microhemorrhages [16]. This imaging modality is based on differences in magnetic susceptibility of different substances in a magnetic field. Deoxygenated hemoglobin, methemoglobin, and hemosiderin have strong paramagnetic properties that can cause local magnetic field inhomogeneity. Hemorrhage causes a drop in signal (hypointensity) on SWI. In addition, SWI was recently shown to detect post-ischemic cerebral hemorrhage within two hours after onset, which indicates its ability to detect HT in the hyperacute phase [17].

Application of ADC values

In recent studies, ADC values were shown to help predict the risk of HT in patients with ischemic stroke [17, 18]. However, the precise nature of the association between ADC values and incidence of HT in these patients is not completely understood. There is a negative correlation between the ADC values and the DWI signals; restricted diffusion of water molecules lowers the ADC values, which manifests as hypointense lesions in the ADC map and hyperintense lesions on DWI.

ADC value is known to reach its nadir within 8-32 hours and to maintain this low value for another 72 hours; MRI examinations should be done within this 72-hour time window. Based on this premise, the study assumes that the

### Table 3. ADC values by study group

<table>
<thead>
<tr>
<th></th>
<th>HT group n = 28</th>
<th>Non-HT group n = 30</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum ADC value (mean ± SD)</td>
<td>384.3 ± 62.3</td>
<td>551.7 ± 73.9</td>
<td>131.5-203.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean ADC value (mean ± SD)</td>
<td>453.9 ± 43.8</td>
<td>620.0 ± 73.0</td>
<td>134.5-197.6</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

HT, hemorrhagic transformation; ADC, apparent diffusion coefficient.
ADC values in the acute phase of cerebral infarction are relatively stable and thus a quantitative comparison can be valid. Additionally, the peak incidence of HT is within 1 to 2 weeks after ischemia [18]. Therefore, the follow-up MR examinations for detecting HT were performed within 2 weeks after admission.

In the current study, statistical analysis showed significantly lower minimum and mean ADC values in the HT group as compared to those in the non-HT group. We believe that the ADC value is expected to be a strong predictor for HT following acute ischemic cerebral infarction.

Studies have sought to determine the ADC threshold compatible with survival of ischemic tissues. Dardzinski et al. studied a rat model of ischemia, and suggested that the ADC threshold of permanent cerebral ischemia in two hours is $550 \times 10^{-6}$ mm$^2$/s [19]. Kazemi et al. blocked the middle cerebral artery for three hours, and found the absolute ADC values associated with necrosis to be $< 470 \times 10^{-6}$ mm$^2$/s [20]. Fiehler et al. studied the frequency of normalization of ADC values that were decreased in hyperacute stroke, and noted that approximately 70%-80% of ADC value is recoverable [21].

Clinical studies and animal experiments have confirmed that the severity of cerebral infarction as well as the occurrence of HT has a direct relationship with the degree and duration of cerebral ischemia. Furthermore, the extent of damage to microvasculature and tight junctions between endothelial cells in the initial 24 hours also reflects the degree of cerebral ischemia. In animal models, ischemic tissues with the minimum ADC values showed the most severe pathophysiological changes and damage to blood brain barrier, which corresponds to a high risk of HT [22-25]. Experiments have also suggested a correlation between decreased ADC values in infarcts (including, minimum and mean ADC values) and HT. A more obvious decrease in ADC values usually indicates a higher risk of bleeding. Moreover, the bleeding area within the infarct mainly corresponds to the area with the lowest ADC value, and is mostly localized in the central area of the infarct; this further illustrates that the central part is most vulnerable to tissue necrosis.

Scholars have used different methods to determine the cut-off values for prediction of HT. Tong et al. measured the ADC values pixel-by-pixel in 17 patients with cerebral infarction within 8 hours of onset. They found that the ADC values in patients with HT were lower than those in patients with no evidence of HT, and that the pixels with ADC value $< 550 \times 10^{-6}$ mm$^2$/s in the HT group (47%) were significantly greater than those in the non-HT group (19%) [26, 27]. In addition, > 40% of the pixels showed ADC values $< 550 \times 10^{-6}$ mm$^2$/s in all infarcts that eventually developed secondary HT. Nevertheless, < 31% of the pixels had ADC values $< 550 \times 10^{-6}$ mm$^2$/s in all non-HT lesions. Derek et al. recommended an ADC threshold of $< 400 \times 10^{-6}$ mm$^2$/s for patients with cerebral infarction who underwent intravenous rt-PA thrombolysis within 7 hours of onset; the pixels of ADC value $< 400 \times 10^{-6}$ mm$^2$/s in the HT group were significantly higher than those in the non-HT group [28].

In the current study, the cut-off level of minimum ADC values for predicting HT was $450 \times 10^{-6}$ mm$^2$/s, and that of mean ADC values was $500 \times 10^{-6}$ mm$^2$/s. The difference between our findings and those reported previously may be due to the following reasons: (1) different time-points of MRI examination: the patients in this study underwent MRI scanning within 3 days after onset of ischemia as many patients reached hospital > 6 hours after onset of symptoms. The time window was only 3-8 hours in the earlier studies; (2) different treatment: patients in this study did not receive any thrombolytic therapy with the exception of anti-platelet therapy, while patients in the earlier studies underwent intravenous thrombolysis.

**Conclusion**

This study indicates that DWI is a useful tool to evaluate acute ischemic infarction, and that the quantitative analysis of ADC values is helpful in the assessment. SWI is a sensitive method to identify secondary HT. The ADC values in infarcts can reflect the degree of ischemia and may be a useful reference for predicting the risk of HT in patients with early ischemic infarction.

**Disclosure of conflict of interest**

None.

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