Prediction of Hemorrhagic Transformation in Acute Ischemic Stroke: Clinical and MR Imaging Study

Abdelhady T. Emam¹, Fatma M. Awad¹, Mohamed Elsayed², Rasha Soliman³
Departments of Radiodiagnosis¹, Neurology², Cairo University; Neurology, Beni-Sueif University³

ABSTRACT

Background and Purpose: Hemorrhagic transformation is a significant complication of acute ischemic stroke. It could be predicted by MR imaging. The goal of this study was to determine the value of various clinical risk factors and MR imaging sequences for the prediction of hemorrhagic transformation (HT) in acute ischemic stroke. Patients and Methods: Forty-five patients with acute ischemic stroke were evaluated clinically using NIHSS scale, brain MR imaging with contrast administration within 6 hours of symptom onset and follow-up CT or MRI within 72 hours was done. DW imaging lesion volumes and ADC values were compared between patients with and those without HT. ADC parameters were compared between lesions with and those without parenchymal enhancement. In patients with early parenchymal enhancement, mean ADCs were obtained in the enhancing area and in the rest of the ischemic lesion. Results: Sixteen patients (35.5%) had HT (12 with hemorrhagic infarction and four with parenchymal hematoma). Patients with HT had decreased mean ADCs and large lesion volumes on DW imaging, but differences were not significant (P> 0.5). HT occurred in 4 patients (100%) with parenchymal enhancement, which corresponded to the site of HT. In enhancing lesions, the ADC ratio (0.77 ± 0.06) was slightly higher and the delay in time to peak (0.11 ± 2.79) was less than respective values in the rest of the ischemic lesion (0.66 ± 0.06 and 8.78 ± 4.85, respectively; P = 0.067). Higher baseline NIHSS score, atrial fibrillation were significantly associated with subsequent HT. Conclusion: Higher baseline disability and AF is highly associated with subsequent HT. DW imaging lesion volumes and ADC values had no strong relationship with HT. Early parenchymal enhancement is highly specific for HT. (Egypt J. Neurol. Psychiat. Neurosurg., 2009, 46(1): 79-86)

INTRODUCTION

Symptomatic hemorrhagic transformation is a severe complication of acute ischemic stroke which occurs at a higher frequency after thrombolysis. Therefore, the identification of risk factors leading to hemorrhage is crucial for effective and safe thrombolytic therapy¹. Different potential risk factors for cerebral hemorrhagic transformation (HT) after thrombolytic therapy have been identified (e.g. age, severity of neurological symptoms, high blood pressure, history of diabetes mellitus, heart disease, lower platelet count, pre-treatment with antiplatelet agents, and early CT abnormalities)². Results of several animal studies suggest that early parenchymal enhancement is observed after reperfusion and damage of the blood brain barrier in ischemic tissue, and that it may enable early prediction of HT³. In their study, Vo et al. suggested that the early parenchymal enhancement may be a good predictor of symptomatic HT in patients with acute ischemic stroke.

The large extent of hypo attenuation on CT was established as a predictive factor for symptomatic hemorrhage, and for the poor outcome after intravenous thrombolytic therapy⁴. However, this finding remains controversial in patients treated within 3 hours⁵,⁶. Reports suggest that stroke MR imaging may be useful in identifying risk factors of hemorrhage that may not be identified on CT¹.

The goal of this study was to determine different potential risk factors (clinical and laboratory) for hemorrhagic transformation, and the value of different MR imaging sequences for the
prediction of hemorrhagic transformation in acute ischemic stroke.

**PATIENTS AND METHODS**

**Patient Selection:**
We retrospectively selected 45 patients who presented within 6 hours after the onset of acute ischemia between January 2005 and April 2008. All patients were fulfilling the following criteria: (1) Acute infarction of the middle cerebral artery (MCA) territory; (2) MR imaging, including gadolinium-enhanced T₁-weighted and DW imaging, within 6 hours of symptom onset; and (3) Follow-up plain CT or MR imaging, conventional gradient-echo (GRE), within 72 hours.

**Imaging Techniques:**
CT scans were obtained before MR imaging in all patients. MR images were obtained using a 1.5-T unit (Signa; GE Medical Systems, Milwaukee, WI). The imaging protocol included DW imaging, T₂-weighted GRE imaging, and contrast-enhanced T₁-weighted imaging.

DW imaging was performed with an echo-planar spin-echo sequence. Twenty transverse sections, tilted along the orbitomeatal line and covering the whole supratentorial brain, were imaged and b values of 0 and 900 or 1000 s/mm². Imaging parameters for DW imaging were as follows: TR/TE = 6500/96.8, matrix = 128 x 128, FOV = 24 x 24 cm, section thickness = 5 mm, intersection gap = 2 mm, and acquisition time = 20 seconds. Three DW images with orthogonally applied diffusion gradients (b value, 1,000 sec/mm²) and a T₂-weighted reference image (b value, 0 sec/mm²) per section were obtained. Effects of diffusion anisotropy were minimized by generating trace images (trace of the diffusion tensor) as the mean of the three DW images.

Enhanced axial T₁-weighted images parameters were as follows: matrix = 256 x 192, FOV = 24 x 24 cm, section thickness = 5 mm, intersection gap = 2 mm, and one excitation. This sequence was performed with the injection of gadopentetate dimeglumine (Gd) 0.2 mmol/kg (Magnevist, Schering, Berlin, Germany) at a rate of 4 mL/s, into an antecubital vein by using an 18-gauge cannula, with an MR imaging-compatible power injector (Spectris; Medrad, Pittsburgh, PA). The bolus of contrast material was followed by a 15-mL bolus of saline at the same injection rate.

**Post processing of the Imaging Data:**
The region of interest (ROI) was manually drawn (hyperintense lesion on each DW imaging section). These ROIs were transferred to the ADC maps. Lesion volumes on DW imaging were measured by drawing regions of interest around the lesions and by multiplying the lesion areas by the section and gap thicknesses. However, the lesion area in the lowermost section was multiplied only by the section thickness. ADC values of voxels in the ROIs were calculated for each patient and a mean ADC value was eventually obtained. In addition, patients were divided into four groups according to the number of voxels with different ADC values and a mean was obtained for each group and compared in patients with and without HT.

We reviewed the MR images to determine the presence of early parenchymal enhancement. Early parenchymal enhancement was defined as a hyperintense area on the initial Gd-enhanced T₁-weighted image, which was noted as the area of the hyperintense lesion on DW images. For quantitative ROI measurement in patients with early parenchymal enhancement, enhanced T₁-weighted images were spatially co-registered to the DW imaging by using SPM2 software. In patients with early parenchymal enhancement, mean ADCs were obtained in the enhancing area and in the rest of the ischemic lesion.

Mean ADC values for patients with and without HT and early parenchymal enhancement were also calculated.

Symptomatic hemorrhage was defined as clinical deterioration with a National Institutes of Health Stroke Scale (NIHSS) score of more than 3 likely due to hemorrhage.

HT was defined and classified into four subtypes, as previously described³,⁹,¹⁰: Hemorrhagic infarct type 1, which was small petechiae along the margins of the infarct. Hemorrhagic infarct type 2, which was more confluent petechiae within the infarcted area but without space-occupying effect. Parenchymal hematoma type 1, which was hematoma in less than 30% of the infarcted area with some space-occupying effect; and parenchymal
hematoma type 2, which was hematoma in more than 30% of the infarcted area with substantial space-occupying effect or any hemorrhagic lesion outside the infarcted area.

Clinical Data:
We reviewed the patients’ clinical data: Baseline neurologic deficits, as assessed by using the NIHSS score and presence of risk factors (history of hypertension; use of an antiplatelet agent or an anticoagulant; cardioembolic stroke risk factors, history of diabetes; and atrial fibrillation).

Statistical Analysis:
Statistical analysis was performed by using (SPSS-PC, version 10.0, 1999; SPSS, Chicago, IL) software. Patients were divided into two groups according to the presence or absence of HT. Differences in MR imaging variables between the groups were assessed by using the Student t-test for continuous variables. Nominal clinical variables between the groups were compared by using Χ² test. Diffusion parameters in the ischemic lesion were compared between lesions with and those without early parenchymal enhancement by using the Wilcoxon signed ranks test. A P value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Forty-five patients (24 men, 21 women), age range, 50–89 years (mean; 68 ± 9.3 years) were selected. Patients presented within 2–6 hours (mean; 4 hours) from the onset of their symptoms to MR imaging. Nine patients presented within 2 hours from the onset of symptoms, with a similar number presenting within 3 and 6 hours. Eight patients presented within 5 hours, and 10 within 4 hours from the onset of symptoms. The time to follow-up imaging ranged from 1 to 3 days (mean; 2.1 days). HT was identified in 16 patients (35.5%) at follow-up: hemorrhagic infarct in 12 patients and parenchymal hematoma in four. Symptomatic hemorrhage was observed in one patient.

Table (1) and (2) show the results of MR imaging:
Comparing patients without HT and patients with HT, the latter had a lower mean ADC, a larger lesion volume on DW imaging, and more voxels with low ADC [the difference was not significant (P > 0.05)].

Early parenchymal enhancement was observed in four patients (8.9%). All patients with this enhancement had HT on follow-up imaging (100%). They had a parenchymal hematoma type 1, hemorrhagic infarct type 2, or hemorrhagic infarct type 1. No early parenchymal enhancement was identified in the patients without HT (P = 0.003). Furthermore, the HT sites corresponded to those with parenchymal enhancement in all patients.

Table (3) shows ADC parameters of the four enhancing lesions:
Mean ADC values and ADC ratios of enhancing lesions were slightly higher than values in the rest of the ischemic lesion, but the difference was not significant (P = 0.068 and P = 0.066, respectively).

The mean initial NIHSS score of 45 patients was 14.9 ± 5.7. In patients with HT, the score was 13.1 ± 6.2, and in patients without HT, it was 9.7 ± 5.8 (P = 0.043). Subsequent HT was noted in the following patients: 8 of 26 with hypertension (P > 0.05), in 3 of 11 receiving an anticoagulant or an antiplatelet agent (P > 0.05), in 8 of 20 with atrial fibrillation (P = 0.047), and in 10 of 22 with a history of diabetes (P > 0.05).

Table 1. DWI lesion volumes, ADC values, and early parenchymal enhancement.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without HT (n = 29)</th>
<th>With HT (n = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWI lesion volume (cm³)</td>
<td>23.4 ± 34.8</td>
<td>51.1 ± 84.9</td>
<td>0.114</td>
</tr>
<tr>
<td>Mean ADC (x 10⁻⁶ mm²/second)</td>
<td>58 ± 78</td>
<td>548 ± 100</td>
<td>0.106</td>
</tr>
<tr>
<td>Gd enhancement</td>
<td>0</td>
<td>4(25.3%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Table 2. Mean number of voxels with different ADC values.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without HT (n = 29)</th>
<th>With HT (n = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voxels with ADC ≤ 550 (x 10^-6 mm^2/second)</td>
<td>721 ± 1076.6</td>
<td>2888.1 ± 8108.9</td>
<td>0.134</td>
</tr>
<tr>
<td>Voxels with ADC ≤ 450 (x 10^-6 mm^2/second)</td>
<td>356 ± 516.9</td>
<td>14056 ± 58467</td>
<td>0.182</td>
</tr>
<tr>
<td>Voxels with ADC ≤ 350 (x 10^-6 mm^2/second)</td>
<td>128.5 ± 230.5</td>
<td>911 ± 2877</td>
<td>0.124</td>
</tr>
<tr>
<td>Voxels with ADC ≤ 250 (x 10^-6 mm^2/second)</td>
<td>33 ± 78</td>
<td>234 ± 672.6</td>
<td>0.093</td>
</tr>
</tbody>
</table>

Table 3. ADC parameters of four enhancing lesions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enhancing lesions (n = 4)</th>
<th>Non-enhancing lesions (n = 41)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ADC (x 10^-6 mm^2/second)</td>
<td>593 ± 63</td>
<td>511 ± 36</td>
<td>0.068</td>
</tr>
</tbody>
</table>

N.B.: Data are the mean ± standard deviation

Fig. (1): 71-years-old male who presented with right hemi paresis and aphasia 2 hours after symptom onset. DW image and ADC map obtained 3 hours after onset of the symptoms show infarction in the left MCA territory. Gd-enhanced T1-weighted image (T1WI) shows a focal enhancing area in the left basal ganglia (arrow). Follow-up...
non-enhanced CT scan (NECT) depicts a small parenchymal hematoma in the left basal ganglia that corresponds to the enhancing area (arrow).

**Fig. (2):** 63 years old female who presented with right hemiplegia 4 hours after symptoms onset. DW image and ADC map obtained 5 hours after onset of the symptoms show infarction in the left MCA territory. Follow-up nonenhanced CT scan (NECT) depicts large parenchymal and intraventricular hemorrhage in the infarcted area.

**Fig. (3):** 61 years old male who presented with aphasia 4 hours after symptoms onset. DW image obtained 5 hours after onset of the symptoms show infarction in the left MCA territory. Contrast enhanced T1 weighted image shows a small enhancing area (arrow). Follow-up nonenhanced CT scan (NECT) depicts parenchymal hematoma in the infarcted area.

**DISCUSSION**

Symptomatic intracerebral hemorrhage still represents the most feared complication of treatment with IV thrombolysis and one of the reasons for the limited use of it\(^1\).

At the same time, it is still uncertain by which means (if at all) patients at high risk of severe
intracerebral hemorrhage after thrombolysis can be identified before the initiation of treatment\(^\text{11}\).

Clinical findings, such as baseline NIHSS score, history of hypertension, anticoagulant use, and cardio-embolic stroke, atrial fibrillation and history of diabetes have been suggested as risk factors for HT in patients with acute ischemic stroke\(^\text{6,12,13}\).

In this study, high baseline NIHSS scores and atrial fibrillation were significantly associated with subsequent HT, compared to the results of previous studies.

With modern MRI sequences such as gradient echo and echo planar susceptibility-weighted imaging, MRI is known to be more sensitive to cerebral micro bleeds or petechial hemorrhage than CT\(^\text{14-16}\).

Contrast enhancement (before treatment) is predictive of the liability to hemorrhage and has a good correlation with the subsequent severity of HT, as shown in an animal study\(^\text{17}\). In one study, two of three patients with early parenchymal enhancement after IV thrombolytic therapy had symptomatic hemorrhage at follow-up\(^\text{17}\). Because IV thrombolytic therapy can aggravate the rapid breakdown of the microvascular barrier, early parenchymal enhancement might be a potential risk factor for post treatment symptomatic hemorrhage\(^\text{18}\).

In this study, HT occurred in all patients with early parenchymal enhancement. This finding was consistent with those of previous animal and human studies regarding correlation between parenchymal enhancement and HT\(^\text{4,18}\).

Regarding other MR imaging parameters used in our study such as ADC values and DW imaging lesion volumes, they were not as reliable as early parenchymal enhancement for predicting HT. This was not keeping with other clinical MR studies which showed that the ADC value of ischemic tissue was predictive of HT\(^\text{19}\). This could be explained by small number of our patients. Also, this may be because of a fogging effect on the ADC value, as reflected by the slightly higher mean ADC ratios found in our patients. This fogging effect may be the result of early vasogenic edema, 2–6 hours after stroke\(^\text{20}\).

It is also as Beauchamp et al.\(^\text{21}\) mentioned, the use of optimal diffusion imaging strategies results in increased conspicuity of ischemic regions and increased reproducibility of diffusion constants between research centers. An understanding of the principles of diffusion imaging and current controversies in the field is necessary for optimal application of this technique in the evaluation and treatment of cerebral ischemia.

We concluded that DW imaging lesion volume and ADC value were not strongly associated with HT. Early parenchymal enhancement was uncommon in patients with acute MCA infarction within 6 hours of symptom onset, but it was highly specific for HT. Moreover, higher baseline scoring of NIHSS and AF are strong clinical predictors of HT.

REFERENCES
الملخص العربي

التنبؤ بحذوث التحول المنزف في الجلطة الدماغية الحادة
دراسة إكلينيكية وباستخدام أشعة الرنين المغناطيسي على المخ

بعد التحول المنزف في جلطة المخ الحادة من المضاعفات الهامة والتي يمكن التنبؤ بها إكلينيكياً وباستخدام أشعة الرنين المغناطيسي على المخ. وتهدف هذه الدراسة إلى تحديد مدى أهمية الفحص الإكلينيكي والتصوير بالأشعة بالرنين المغناطيسي على المخ بالطرق المختلفة للتنبؤ بحذوث التحول المنزف في حالات جلطات المخ الحادة.

تمت هذه الدراسة على 45 مريضاً من مرضى الجلطات الدماغية الحادة، الذين تم فحصهم إكلينيكيًا وعمل أشعة بالرنين المغناطيسي على المخ بالصفحة خلال 6 ساعات من ظهور الأعراض وأخذ أشعة أخرى مقاطعة أو بالرنين المغناطيسي على المخ خلال 72 ساعة. وتم مقارنة حجم الإصابة في تصوير تشعة الأشعة ومعامل التشعة في مرضى التحول المنزف، وهولاء بدون تحول منزف بجلطة المخ.

وأثبت النتائج أن 16 مريضاً (35.5%) حدث لهم تحول منزف (12 جلطة منزفة و4 نزيف في السيف الحشوي). وجد أن المرضى الذين حدث لهم تحول منزف يعانون أكثر من تدهور الحالة الإكلينيكية، وأن حجم الإصابة كان أكبر في تصوير تشعة الأشعة، وأن معامل التشعة كان أقل ولكن هذه الفروق لم تصل بعد إلى النتائج الإحصائية.

ومن هنا نستنتج أن حجم الإصابة في تشعة الأشعة وقيمة معامل التشعة لا يوجد لها علاقة قوية بحذوث التحول المنزف بجلطة المخ، وأن الوضوح الحشوي المبكر يرتبط بعلاقة قوية بالتحول المنزف لجلطة المخ الحادة.