Prediction of Hemorrhagic Transformation Following Acute Stroke

Role of Diffusion- and Perfusion-Weighted Magnetic Resonance Imaging

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Background: Acute diffusion-weighted (DWI) and perfusion-weighted (PWI) magnetic resonance imaging (MRI) findings may correlate with secondary hemorrhagic transformation (HT) risk in patients with stroke. This information could be of value, particularly in individuals being considered for thrombolytic therapy.

Objective: To determine the relationship between DWI and PWI findings and the risk of secondary HT in patients with acute stroke.

Design: Retrospective case series.

Setting: Academic medical center.

Patients: Twenty-seven patients with acute stroke capable of being evaluated with DWI/PWI 8 hours or less after symptom onset.

Main Outcome Measures: Apparent diffusion coefficient values, perfusion delay measurements, and subsequent MRI or computed tomographic scans detected HT.

Results: The mean ± SD apparent diffusion coefficient of ischemic regions that experienced HT was significantly lower than the overall mean ± SD apparent diffusion coefficient of all ischemic areas analyzed (0.510 ± 0.140 × 10⁻³ mm²/s vs 623 ± 0.113 × 10⁻³ mm²/s; P = .004). This difference remained significant when comparing the HT-destined ischemic areas with the non-HT-destined areas within the same ischemic lesion (P = .02). Patients receiving recombinant tissue-type plasminogen activator (rt-PA) experienced HT significantly earlier than patients not receiving rt-PA (P = .002). Moreover, a persistent perfusion deficit in the area of subsequent hemorrhage at 3 to 6 hours after the initial MRI scan was identified in significantly more patients who experienced HT than in those who did not (83% vs 30%; P = .03).

Conclusion: Both DWI and PWI scans detect abnormalities that are associated with HT. These findings support a role for MRI in identifying patients who are at increased risk for secondary HT following acute ischemic stroke.

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Recent evidence suggests that early use of thrombolytic agents can have a substantial positive impact on neurological outcome following acute ischemic stroke. However, there remains significant controversy regarding the relative risks and benefits of thrombolytic therapy. Although some clinical and radiographic characteristics have retrospectively been associated with subsequent neurological outcome, it remains difficult to determine which patients will benefit most from treatment. One of the most significant problems impeding the general use of thrombolytic therapy is concern over the risk of secondary intracranial hemorrhage. Thus, a method that could identify patients at higher risk for intracerebral hemorrhage might be helpful in improving the risk-benefit ratio of thrombolytic therapy.

In the past few years, both diffusion-weighted (DWI) and perfusion-weighted (PWI) magnetic resonance imaging (MRI) have been used to detect ischemic tissue injury earlier than conventional neuroimaging modalities in both experimental and clinical settings. In addition, DWI and PWI lesion volumes correlate with early functional outcome and are influenced by thrombolytic administration. If DWI and PWI could also identify patients at increased risk of subsequent intracranial hemorrhage, this could further add to the utility of MRI in acute stroke.

In this study, the relationship between DWI, PWI, and secondary hemorrhagic transformation (HT) was assessed.
PATIENTS, MATERIALS, AND METHODS

Patients receiving a DWI/PWI scan within 8 hours and another computed tomographic (CT) or MRI scan within 1 week after symptom onset were candidates for study. Some patients were participants in previous studies of DWI and PWI reported from this institution. Patients treated with recombinant tissue-type plasminogen activator (rt-PA) (n=16) or putative neuroprotective agents (n=14) were eligible. Informed consent was obtained in all cases, and the protocol was fully approved by the local ethics committee.

Data regarding clinical characteristics of patients were obtained from review of the patients’ medical records. Patients received serial follow-up CT or MRI scans for up to 1 week after symptom onset to detect HT unless the patient died before that time or experienced neurological deterioration requiring an urgent CT scan (patients 12, 13, 14, and 16). Scans were performed at 3 to 6 hours (T2), 24 to 36 hours (T3), and 5 to 7 days (T4) after presentation (T1).

Diffusion-weighted imaging and PWI were performed using echo planar imaging on a 1.5-T General Electric Signa system (General Electric Company, Fairfield, Conn.). Areas of ischemia were identified as regions of hyperintensity on the initial DWI images. A region of interest was hand drawn to encompass the area of abnormal DWI using specialized software (MRVision, Menlo Park, Calif.). Each region of interest was then transferred to its corresponding ADC map. The average ADC value of the region of interest was then calculated. The ADC value of the entire lesion was then determined by taking the weighted average of the ADC values for each individual MRI slice containing an ischemic region and accounting for the area of each slice involved. The ADC values of the regions that subsequently experienced HT were generated by identifying areas of hemorrhage on each slice of the follow-up MRI or CT scan and using these regions of interest on the initial ADC maps.

Perfusion-weighted imaging was performed using dynamic susceptibility contrast-enhanced MRI. Gradient echo single-shot echo planar imaging was performed using gadolinium (0.1 mmol/kg) with 35 to 40 time points obtained over 12 slices with a 3-mm slice thickness and a 2.5-mm gap between slices. Other parameters were the same as those for DWI. Perfusion images were processed to generate time-to-peak maps. Regions of interest were determined visually and then handtraced. The magnitude of the perfusion delay was determined using the method of Neumann-Haefelin et al.

Hemorrhagic transformation was identified using previously described criteria (Figure 1). In general, any area of heterogeneous or homogenous hypointense (dark) signal within the area of ischemia on a T2-weighted (b=0) or DWI slice more than 1 cm² in size was considered hemorrhagic. The abnormal signal could not solely include regions of MRI susceptibility artifact and had to be present on at least 2 different MRI sequences. The presence of an abnormal signal on more than 1 slice was preferred, but not essential. In cases in which a susceptibility-weighted sequence (ie, gradient recall echo [GRE]) was available (n=8), the hemorrhagic region had to be detected on that sequence. Computed tomographic–detected hemorrhage was defined as a heterogeneous or homogenous high signal on a noncontrast CT scan within the area of infarction not associated with artifact or calcification. Symptomatic hemorrhage transformation (SHT) was defined as bleeding associated with an increase in National Institutes of Health Stroke Scale (NIHSS) score of 1 point or higher. Asymptomatic hemorrhagic transformation (AHT) was defined as evidence of bleeding on MRI or CT scan without clinical evidence of neurological deterioration. Patients experiencing HT at the initial time point (patients 14 and 16, Table) were excluded from this ADC analysis since in these cases the presence of HT could contaminate the ADC measurements. In addition, because the purpose of this study was to predict subsequent hemorrhage, measurement of ADC in these individuals with early HT was not felt to be helpful because the hemorrhage had already occurred. All MRI measurements were performed in a blinded manner.

Early reperfusion was defined as complete resolution of the PWI abnormality in 36 hours or less after initial MRI scan. The presence or absence of PWI abnormality and the time to resolution were recorded and compared with the rate of subsequent hemorrhagic change. Perfusion delay was defined as a delay of 1 second or more compared with that of the contralateral hemisphere.

All patients had their neurological deficit scored initially and 30 days after symptom onset by a stroke neurologist certified in the use of NIHSS. Patients who died before 30 days were assigned a final maximum NIHSS score of 42.

Statistical analyses were performed using computerized software (SigmaStat; Jandel Scientific, San Rafael, Calif.). χ² Analysis and the Fisher exact test were used for analysis of contingency tables as appropriate. Significance was determined at the P<.05 level.

RESULTS

PATIENT CHARACTERISTICS

Between August 1996 and January 1999, 455 patients with a final diagnosis of ischemic stroke were admitted to the Stanford Stroke Center’s inpatient Stroke Service, Palo Alto, Calif. Of these, 27 patients (6%) were identified who fulfilled inclusion criteria (Table). There were 16 men and 11 women. The mean±SD age for all participants was 70±13 years. The mean±SD initial NIHSS score was 11±7, and the mean±SD time to MRI scan was 5 hours 5 minutes±1 hour 16 minutes.

In most patients (n=22), MRI was performed serially between T2, T3, and T4 after T1. In 3 cases (patients 13, 14, and 16; Table), a follow-up CT scan was performed instead of MRI owing to neurological deterioration. One patient (patient 12) died before the second cerebral scanning was performed.

Sixteen subjects received rt-PA and 11 did not (Table). There was no significant difference in initial or final NIHSS...
score, age, or time to initial MRI scan between the rt-PA–treated and non–rt-PA–treated patients. In addition, 14 (52%) of 27 patients also participated in placebo-controlled neuroprotective agent trials (palmafene [Cervene; Baker Norton, Miami, Fla], n = 7; lubeuluzole [Prosnap; Janssen Research Foundation, Beerse, Belgium], n = 4; fibroblast growth factor [Fiblast; Scios Nova, Mountain View, Calif], n = 2; or aptiganel [Cerestar; Bowhringer, Ingleheim, Ridgefield, Conn], n = 1). The mean ± SD time to rt-PA treatment was 2 hours 6 minutes ± 3 minutes after symptom onset. There was no significant difference in time to treatment, age, sex, or NIHSS scores between patients treated with intravenous (n = 14) or intra-arterial (n = 2) therapy. In all cases, rt-PA was administered before the MRI scan was performed.

Magnetic resonance imaging or CT evidence of intracranial blood was detected on follow-up scans in 16 of 27 patients: 9 (56%) of 16 treated with rt-PA and 7 (63%) of 11 not treated with rt-PA. A susceptibility-weighted sequence (GRE) was performed in 8 (30%) of 27 patients. In all GRE-evaluated cases, the hemorrhage detected on DWI or T2-weighted imaging (b = 0) was apparent on GRE.

Three patients (19%) in the rt-PA–treated group experienced SHT compared with none in the non–rt-PA–treated group (P = .24). Hemorrhagic transformation was detected by T3 after symptom onset in 1 (16%) of 6 non–rt-PA–treated patients compared with 9 (100%) of 9 in the rt-PA–treated group (P = .002). Patients experiencing SHT had significantly worse outcomes than patients experiencing AHT (final respective NIHSS score, 31 vs 9; P = .04). However, between patients with and without HT there was no significant difference in initial NIHSS scores (10 in both groups; P = .52) or final scores (11 vs 9; P = .27).

ADC AND HT

Apparent diffusion coefficient values were successfully obtained in 26 (96%) of 27 patients between T1 and T4. In 1 patient (patient 26, Table), an ADC measurement obtained in 26 (96%) of 27 patients between T1 and T4.

The mean ± SD ADC for all ischemic lesions was 0.623 ± 0.114 × 10⁻³ mm²/s. The mean ADC was lower in lesions experiencing secondary hemorrhage compared with those that did not, though this did not reach statistical significance (0.606 ± 0.119 × 10⁻³ mm²/s for HT vs 0.640 ± 0.114 × 10⁻³ mm²/s for non-HT–destined lesions; P = .15). However, the ADC of the ischemic subregions that subsequently demonstrated hemorrhage change was significantly lower than the average ADC of all ischemic regions in the study (0.510 ± 0.140 × 10⁻³ mm²/s vs 0.623 ± 0.113 × 10⁻³ mm²/s; P = .004). Similarly, the mean ± SD ADC of HT-destined subregions on the initial DWI scan was significantly lower than the mean ± SD ADC of the HT-destined ischemic areas as a whole (0.510 ± 0.140 × 10⁻³ mm²/s vs 0.606 ± 0.120 × 10⁻³ mm²/s; P = .02). In all but 1 case, the ADC of the HT-destined subregion was lower than the ADC for the entire ischemic lesion in the same patient (Figure 2).

The mean ± SD initial ADC of the rt-PA–treated lesions was significantly greater than the mean ± SD ADC of the non–rt-PA–treated lesions (0.650 ± 0.116 × 10⁻³ mm²/s vs 0.538 ± 0.042 × 10⁻³ mm²/s; P = .002). Similarly, the ADC of the rt-PA–treated patients who developed hemorrhage was nonsignificantly greater than the ADC of the non–rt-PA–treated patients who developed hemorrhage (0.546 ± 0.141 × 10⁻³ mm²/s vs 0.409 ± 0.070 × 10⁻³ mm²/s; P = .10). The ADC of patients receiving rt-PA and experiencing HT was also nonsignificantly greater than the ADC of patients not receiving rt-PA and experiencing HT (0.610 ± 0.125 × 10⁻³ mm²/s vs 0.542 ± 0.049 × 10⁻³ mm²/s; P = .37).

The mean lesion volume was greater in the non–rt-PA–treated patients than the rt-PA–treated patients, although this was not statistically significant (47.6 cm³ vs 27.5 cm³; P = .18). In addition, the mean volume of the HT-destined lesions was greater than the non-HT–destined lesions (49 cm³ vs 18 cm³; P = .06).

DELAYED PERFUSION AND RISK OF SECONDARY HEMORRHAGE

Perfusion-weighted imaging was successfully performed between T1 and T3 in 22 (81%) of 27 patients: 12 (69%) of 16 rt-PA–treated and 10 (91%) of 11 non–rt-PA–treated. Of these patients, 12 (6 rt-PA–treated, 6 non–rt-PA–treated) experienced secondary HT, and 10 did not.

Figure 1. Basal ganglia hemorrhagic transformation (HT) associated with low apparent diffusion coefficient (ADC). A, The ADC map of acute infarct 4 hours after symptom onset. Note lower (darker) ADC value in left basal ganglia in region of subsequent hemorrhagic change (arrow). B, Hemorrhagic transformation of the same region of initial low ADC 7 days after symptom onset (arrow). C, Color-enhanced ADC map depicting the same low ADC region on initial magnetic resonance image scan (arrow). Darker colors indicate lower ADC values. D, Color-enhanced map of basal ganglia hemorrhage depicted in B (arrow). Low signal indicates hemorrhagic change. The hemorrhage was asymptomatic (ie, no change in National Institutes of Health Stroke Scale score).
Delayed perfusion was identified initially (T1) in 11 of 12 patients that subsequently experienced HT compared with 6 of 10 patients that did not subsequently experience HT ($P = .14$, Figure 3 and Figure 4). By T2, delayed perfusion was still present within the area of subsequent HT in 10 (83%) of 12 HT-destined patients. In contrast, PWI delay at T2 was detected in only 3 (30%) of 10 patients that did not experience subsequent HT ($P = .03$).

Early resolution of PWI deficit (ie, by T3) was identified in 12 (67%) of 18 patients. There was no significant difference between rt-PA–treated (8 [80%] of 10) and non–rt-PA–treated (4 [50%] of 8) patients ($P = .32$). Of these patients, 8 (75%) of 12 developed hemorrhagic change compared with 4 (66%) of 6 patients who did not have early resolution of their PWI deficit ($P > .99$). There was no significant relationship between time to PWI resolution and NIHSS score at either T1 or at 30 days. In addition, there was no relationship between early PWI resolution and initial ADC values ($P = .59$).

**COMMENT**

To most clinicians, one of the most important concerns regarding the use of rt-PA in acute ischemic stroke is the risk of intracranial hemorrhage. If symptomatic, such hemorrhage may be associated with increased morbidity and mortality.6-8,25-28 Therefore, a method that might identify individuals at increased risk for intracranial hemorrhage could potentially be of substantial aid in clinical management.

In this study, ischemic subregions destined for HT initially registered significantly lower ADC values than non-HT–destined regions. This finding supports our previous observations using a frequency-based ADC analysis.19 However, in that study the individual subregions experiencing HT were not directly assessed. Instead, the percentages of pixels with ADC values below a specific threshold were compared. In contrast, this study directly compared the ADC values of the HT and non-HT–bound subregions. By performing such a direct analysis, the relationship between low ADC values and secondary HT can be established more definitively.

This relationship was not due to a greater volume of ischemic tissue in the rt-PA–treated patients; the volume of ischemic tissue was greater in the non–rt-PA–treated patients. Similarly, it was not due to a lower baseline ADC in the rt-PA–treated patients because the mean ADC of the rt-PA–treated patients was actually greater than the mean ADC of the non–rt-PA–treated patients. In addition, although larger ischemic lesions are associated with HT, we have previously reported that both large and small lesions may experience HT, indicating that size...
alone is an imperfect measure of HT risk.\textsuperscript{59} Larger lesions generally have a greater area of low ADC, which makes them more susceptible to hemorrhage, but smaller lesions can also experience HT, and large lesions may not.

Lower ADC values have previously been hypothesized to represent tissue that is more ischemic and therefore more severely injured.\textsuperscript{29-32} More severely injured tissue may be at greater risk for bleeding due to a variety of factors, particularly disruption of the blood-brain barrier.\textsuperscript{33} Such early evidence of blood-brain barrier breakdown has been reported in both animals\textsuperscript{34-37} and humans.\textsuperscript{38,39}

The ADC findings also suggest the need for more detailed analysis of ischemic lesions. Obtaining average ADC values for the entire ischemic lesion may be insufficient to accurately identify important variations among different regions of the ischemic lesion. Such variations may need to be accounted for in future investigations using DWI. Although there are statistically significant differences in the ADC values between hemorrhagic areas and the ischemic lesion as a whole, it is difficult to identify these variations in ADC by visual inspection alone. Color maps or other visual aids may be more effective at identifying these regions of low ADC values in the future (Figure 1).

Patients receiving rt-PA initially had significantly greater ADC values than patients not receiving rt-PA, which is consistent with prior observations.\textsuperscript{59} The cause of this early ADC increase is unclear, but it may be due to early reperfusion or perhaps a specific effect of rt-PA treatment itself. However, there was no significant relationship between initial ADC values and subsequent normalization of PWI (\(P = .59\)), although the small numbers make definitive conclusions problematic. Thus, it remains unclear what accounts for this early ADC rise. Only studies in which ADC levels are measured both before and after rt-PA treatment might help answer this question.

A relationship between HT and persistent delayed perfusion was also identified. Significantly more patients with persistent delayed perfusion identified at T2 experienced HT compared with those who did not experience delayed perfusion on initial scan (83\% vs 30\%; \(P = .03\)). These findings are consistent with previous positron emission tomography and single-photon emission computed tomography studies that have found a relationship between delayed perfusion and secondary hemorrhage.\textsuperscript{40-42} This relationship may be related to increased blood-brain barrier breakdown due to more severe ischemia in areas of very low perfusion.\textsuperscript{33,34,38,39} In addition, these functional studies have suggested that perfusion findings may potentially aid in predicting the outcome of thrombolytic therapy. Ueda et al.\textsuperscript{40} for example, recently reported that a residual cerebral blood flow greater than 55\% of normal was associated with good outcome.
from rt-PA treatment, while cerebral blood flow less than 35% of normal was associated with poor outcome.

Several previous studies have also shown that early reperfusion with thrombolytic therapy can rescue ischemic tissue from permanent infarction,1,17,45 even if below the usual threshold for tissue viability.44,45 This reduction in lesion volume would be expected to reduce the risk of HT. Therefore, in theory, very early reperfusion could be associated with a decreased risk of HT. Reperfusion after this hyperacute period, however, may be more likely to cause HT owing to reperfusion of ischemic tissue with blood-brain barrier breakdown.33 It follows that the more persistent the perfusion deficit, the greater the likelihood of blood-brain barrier breakdown and the higher the chance of secondary HT.

Because all rt-PA–treated patients underwent MRI after treatment, we cannot be sure if a pretreatment DWI/PWI study would have altered the observed findings. Only studies in which both pretreatment and posttreatment DWI/PWI are performed may adequately address this question. Nevertheless, these findings do suggest that failure to adequately reperfuse ischemic tissue early on may lead to an increased risk of HT. The findings in this study also suggest that rt-PA treatment may exacerbate the tendency toward hemorrhage because rt-PA–treated patients experienced significantly earlier HT than non–rt-PA–treated patients (P = .002).

The relationship between AST and SHT is controversial. Some authors have suggested less clinical relevance for AHT vs SHT.46 Moreover, recent studies of the natural history of HT following thrombolytic therapy suggest that prognosis is worse in patients with SHT than in patients with AHT.6,9,10,25 However, this may be a semantic point, since by definition AHT does not cause neurological decline, while SHT must result in neurological worsening. It seems more likely that the difference between symptomatic and asymptomatic hemorrhage would be related to the degree of bleeding rather than differences in pathophysiology.35,57 In this study, only 3 patients experience SHT, and PWI was completed successfully only in 1 of these patients. Although a perfusion delay was detected in the area of subsequent hemorrhage, it is not possible to draw any firm conclusions on the applicability of these findings to patients with SHT in general, based on only a single patient. Further studies evaluating more patients with SHT alone will be necessary to clarify this issue. However, such studies may be limited by the relatively low frequency of symptomatic hemorrhage in patients treated with thrombolytics. Pooled or multicenter observational studies may be necessary to provide adequate numbers to derive any more definitive conclusions.

CONCLUSIONS

We conclude that secondary HT following acute ischemic stroke is associated with distinctive DWI and PWI characteristics. Regions experiencing secondary HT possess a significantly lower initial ADC than areas not destined to hemorrhage. Moreover, ischemic areas destined to HT are associated with persistent hyperperfusion on PWI. Thrombolytic treatment may enhance HT because patients receiving rt-PA treatment experience hemorrhage significantly earlier than patients not receiving thrombolytics. These findings suggest a potential role of DWI and PWI not only in the identification of cerebral tissue at risk for ischemic infarction, but also for hemorrhagic change.

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