Cerebral Infarction: Time Course of Signal Intensity Changes on Diffusion-Weighted MR Images

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OBJECTIVE. The objective of this study was to determine the time course of signal intensity changes on diffusion-weighted MR images after cerebral infarction.

MATERIALS AND METHODS. Echoplanar diffusion-weighted MR images were obtained at 1.5 T in 212 patients referred for suspected cerebral infarction over a 6-month period. Of those patients, 85 met strict criteria for inclusion in this study: final clinical diagnosis of stroke, reliable timing of clinical ictus by history, and neurologic symptoms persisting longer than 48 hr after onset. Using adjacent or contralateral normal brain for comparison, diffusion-weighted images were visually analyzed retrospectively to evaluate for abnormalities in signal intensity. Because three patients were scanned on two occasions and five patients had two anatomically separable infarctions, 93 reliably dated brain lesions were analyzed.

RESULTS. Diffusion-weighted images showed abnormal findings in 13 (100%) of 13 lesions less than 1 day old, 46 (96%) of 48 lesions 1–4 days old, 16 (94%) of 17 lesions 5–9 days old, three (60%) of five lesions 10–14 days old, and zero (0%) of 10 lesions more than 14 days old.

CONCLUSION. Abnormal signal intensity was present on all diffusion-weighted MR studies obtained in patients within 24 hr of acute cerebral infarction and in up to 94% of patients scanned during the first 2 weeks after ictus. The percentage of abnormal diffusion studies declined with time, and no signal intensity abnormality was seen in stroke patients scanned more than 2 weeks after symptom onset.

Cerebral infarction is the most common cause of disability among adult Americans, with an overall prevalence of approximately 800 cases per 100,000 people. Nearly 500,000 new strokes are diagnosed each year in the United States, and despite a significant decrease in stroke-related mortality over the past 30 years, stroke remains the third leading cause of death [1–5].

MR imaging is the most sensitive technique available to diagnose acute cerebral infarction. The sensitivity of MR imaging for stroke detection may be enhanced through the use of gadolinium contrast material, fluid-attenuated inversion recovery (FLAIR) sequences, and, more recently, diffusion-weighted imaging [6–20].

Diffusion-weighted imaging is a method of MR scanning that uses powerful imaging gradients coupled with rapid spin-echo or echoplanar data acquisition techniques available on modern MR scanners. Because the gradients accentuate phase differences between mobile protons in regions where diffusion rates are relatively high, diffusion-weighted sequences tend to suppress MR signal intensity from CSF and normal brain. Conversely, tissues that have more restricted diffusion of water (such as areas of acute cerebral infarction) typically appear hyperintense on diffusion-weighted images.

The accuracy of diffusion-weighted imaging in the diagnosis of acute cerebral infarction is well established [15–20]. However, relatively little is known about the time course of signal intensity changes on diffusion-weighted images after cerebral infarction. How long do these signal intensity changes last? Can they be used to estimate the age of a cerebral infarction?

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Materials and Methods

Over a 6-month period in 1997, 212 patients with clinically suspected acute cerebral ischemia were referred for MR imaging. All patients were studied on a standard clinical 1.5-T echoplanar MR scanner (Signa; General Electric Medical Systems, Milwaukee, WI) using conventional unenhanced and enhanced imaging sequences as well as an echoplanar diffusion-weighted sequence.

The conventional portion of the MR examination included an unenhanced sagittal 6-mm-thick T1-weighted (TR/TE, 600/15) spin-echo localizer, an unenhanced axial 5-mm-thick fast-spin-echo T2-weighted sequence (3000/100), and an unenhanced coronal 4-mm-thick fast FLAIR sequence (TR/effective TE, 8000/112; inversion time, 2700 msec). Axial and coronal 5-mm-thick T1-weighted (TR/TE, 600/15) spin-echo images were obtained after IV administration of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ).

Between the unenhanced and enhanced portions of the study, a single-shot spin-echo echoplanar diffusion-weighted imaging sequence was obtained using a prototype diffusion acquisition software package (EchoPlus; General Electric Medical Systems). Acquisition parameters included 10,000/96.8 (TR/TE), one excitation, a 30-cm field of view, a 128 × 128 matrix, and a 5-mm section thickness with a 2.5-mm gap. Diffusion gradients were sequentially activated in each of the three principal anatomic axes so that three sets of images sensitive to diffusion in the x-, y-, and z-planes were generated. Gradient strengths corresponding to b-values (diffusion sensitivities) of 0 and 1000 sec/mm^2 were used. Twenty axial images covering the entire brain were obtained in 40 sec.

After the 6-month period of data acquisition was completed, medical records of the 212 subjects were reviewed to select a subset of patients who met the following strict inclusion criteria: definite clinical diagnosis of stroke, reliable timing of clinical ictus by history, and neurologic symptoms persisting longer than 48 hr after onset.

Applying these strict clinical inclusion criteria, we identified 85 patients with clinically definite cerebral infarctions for which the exact time of symptom onset was known. This population consisted of 39 male patients and 46 female patients ranging in age from 10 to 90 years (mean, 67 years). Two patients were scanned on two different occasions, and four patients had two anatomically separate regions of infarction that could be dated separately. One patient with two anatomically and temporally distinct infarcts was scanned on two separate occasions. Accordingly, diffusion-weighted examinations of 93 separate brain lesions were subjected to analysis.

TABLE 1 Diffusion Imaging Findings Relative to Age of Infarct

Time (days)	No. of Patients	No. of Lesions	No. of Diffusion Abnormalities	% Positive Diffusion Scans
<1	12	13	13	100
1–4	44	48	46	96
5–9	16	17	16	94
10–14	4	5	3	60
15–19	4	4	0	0
≥20	5	6	0	0
Total	85	93	78	

The time between MR imaging and the clinical ictus for the 93 lesions appears in Table 1. We rounded the interval between onset of symptoms and MR imaging to the nearest day. Twelve examinations (13 lesions) were performed within 24 hr of symptom onset (the earliest was at 10 hr); 44 examinations (48 lesions) were performed between days 1 and 4; 16 examinations (17 lesions), between days 5 and 9; four examinations (five lesions), between days 10 and 14; and nine examinations (10 lesions), after day 15.

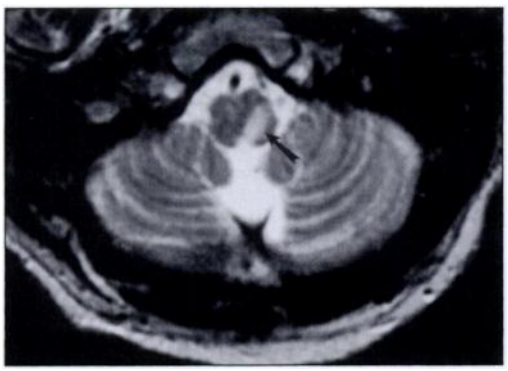
The conventional MR sequences and diffusion-weighted images were reviewed in conjunction with relevant clinical history by two board-certified neuroradiologists. Location was recorded for each signal intensity abnormality that could reasonably account for the patient's symptoms. Signal intensity abnormalities noted on T2-weighted images, FLAIR, and diffusion-weighted images were graded on a binary scale by consensus of the two observers. A score of +1 was assigned to lesions with signal intensity greater than normal adjacent or contralateral brain. A score of 0 was assigned to lesions isointense or hypointense to normal brain. In three cases, a disagreement in scoring between the two original observers occurred and was resolved by showing the image to a third neuroradiologist who was unaware of infarct age and history.

Results

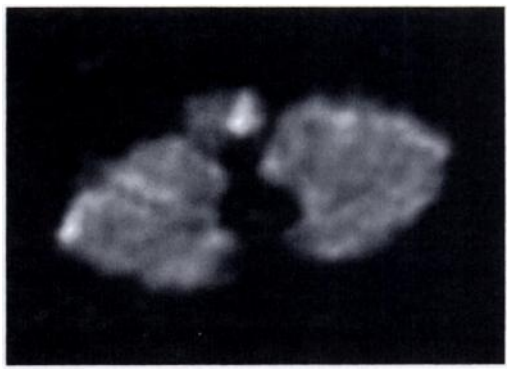
All 13 lesions in the 12 stroke patients studied within 24 hr of clinical ictus had abnormally increased signal intensity on diffusion-weighted images. One of those 13 lesions (scanned 14 hr after clinical ictus) had no signal intensity abnormality on either the FLAIR or the T2-weighted images.

In the 44 patients studied between days 1 and 4, abnormally high signal intensity was seen in 46 (96%) of the 48 distinct cerebral lesions noted. The results of two examinations were false-negative.

The percentage of abnormal diffusion-weighted images decreased as a function of time after clinical ictus (Table 1). The oldest nonhemorrhagic infarct in our series with high signal intensity on diffusion-weighted images was scanned at 14 days (Fig. 1). None of the 10 infarctions scanned 15 or more days after clinical ictus was hyperintense on diffusion-weighted images. In one patient imaged at days 1 and 15 after ictus, the initial diffusion abnormality reverted to normal by the time of the second study (Fig. 2).



A



B

Fig. 1.—60-year-old man with right-sided weakness.
A, Axial T2-weighted MR image obtained 14 days after onset of symptoms shows abnormally increased signal intensity (*arrow*) in left medulla.
B, Axial diffusion-weighted MR image obtained at same time as **A** shows similar region of abnormal signal intensity.

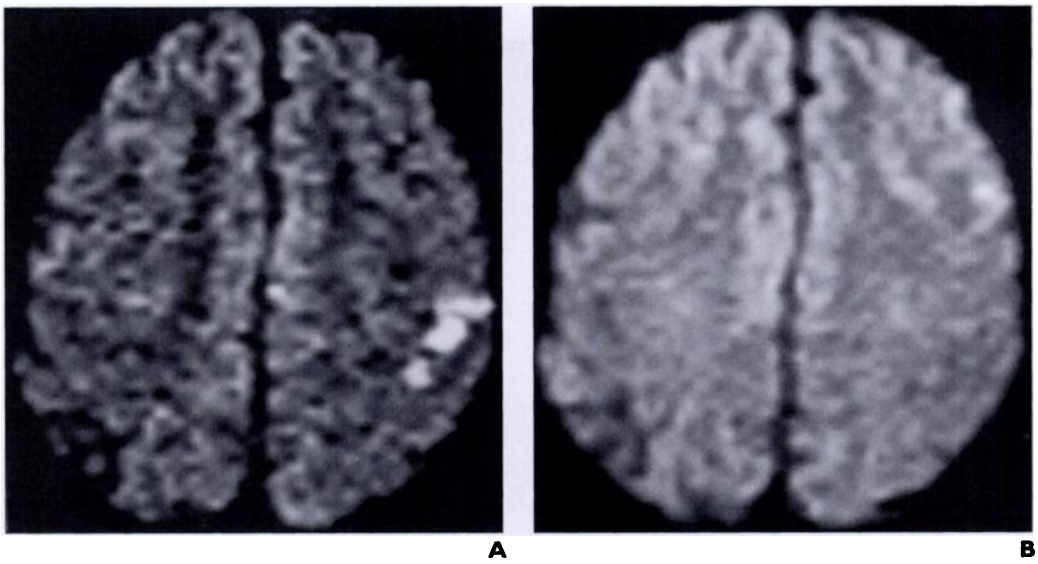


Fig. 2.—67-year-old man with right-sided facial weakness and slurred speech.
A, Axial diffusion-weighted MR image obtained 1 day after onset of symptoms shows large area of hyperintensity in left frontal lobe.
B, Axial diffusion-weighted MR image obtained 15 days after clinical ictus (14 days after **A**) shows that infarcted area is isointense with adjacent brain parenchyma.

The infarctions of 10 patients in our study had undergone hemorrhagic transformation at the time of imaging, manifested either by low signal intensity on T2-weighted images or by high signal intensity on unenhanced T1-weighted images. Five of these patients had scattered areas of punctate (petechial) hemorrhage. The other five had frank parenchymal hematomas of diameter greater than 2.5 cm.

The imaging findings in two of these patients with large parenchymal hematomas deserve special consideration. In both of these patients (scanned at 13 and 20 days, respectively), high signal intensity on diffusion-weighted images was confined to the region of methemoglobin within the center of the hematoma. Signal intensity in the overlying infarcted cerebral cortex was normal (Fig. 3). For scoring purposes, these two patients were judged not to have a diffusion abnormality within the nonhemorrhagic portion of the infarction.

Discussion

After LeBihan et al. [21] first described the technique, numerous investigators used diffusion-weighted imaging to evaluate cerebral ischemic disease [8–23]. Most of that diffusion imaging research has been directed at identification of early cerebral infarction. Using diffusion-weighted imaging, Mintorovich et al. [13] were able to identify infarcts within 15 min of experimental vascular occlusion.

Instead of evaluating diffusion-weighted images, several investigators have used stepped gradient techniques to estimate the apparent diffusion coefficient (ADC) in cases of cerebral infarction. Reith et al. [22] found changes in ADC values within 5 min of ischemia onset. Schlaug et al. [23] showed reduction, pseudonormalization, or even elevation of ADC values after the seventh day after infarction. Lutsep et al. [18] showed that ADC values remained low for the first week after infarction and normalized or became elevated at more chronic time points. Warach et al. [15] and Marks et al. [20] both found that after the initial decrease in the acute stroke period, ADC values gradually increased and became elevated after 10 days. In each of these studies, investigators followed changes in ADC values over time. Although calculation of ADC values yields quantifiable results, it currently requires more time-consuming and complicated data processing that may not be clinically practical for many MR imaging centers. Visual assessment of diffusion images is uncomplicated and faster. Moreover, it requires little more than searching images for subtle differences in signal intensity, a task to which radiologists are well suited.

Using simple visual analysis of diffusion-weighted images, we found that areas of cerebral infarction may have persistent high signal intensity as long as 14 days after clinical ictus. In accordance with the findings of other investigators, we found that the signal intensity of the diffusion abnormality decreases with time and reverts to normal by the end of the second week. Our slightly longer estimate for the duration of a diffusion abnormality compared with some other reports [15, 18, 20, 23] may relate to several factors: our subjects were humans, not animals; our infarctions were clinically, not experimentally, induced; we used slightly different gradient strengths and pulse sequences; and we analyzed signal intensity changes on diffusion-weighted images, not changes in the diffusion constant per se.

The last item deserves further comment. We emphasize that the time course of MR signal intensity changes in cerebral infarction using diffusion-weighted images was studied. Just as a T2-weighted image is not a simple map of T2 values [24], a diffusion-weighted image is not a simple map of diffusion constants. Because diffusion-weighted images are produced using a modified spin-echo pulse sequence with long TR and TE values, the overall signal intensity on diffusion-weighted images reflects not only changes in the diffusion constant but also changes in spin density and T2. This effect, sometimes referred to as "shine through," is well recognized in a variety of other MR imaging applications [24, 25]. Therefore, T2 shine through is another possible reason for the prolonged duration of abnormal signal intensity on our diffusion-weighted images compared with earlier reports. Creation of ADC maps would have eliminated that T2 contribution to lesion signal intensity; however, doing so would have added a step to image processing that may not be available at all sites performing diffusion imaging.

Two diffusion-weighted studies in our series had false-negative results in patients scanned within 48 hr of the onset of symptoms. The first occurred in a patient who presented with a 1-day history of visual changes and right-sided limb weakness. The results of conventional and diffusion-weighted im-

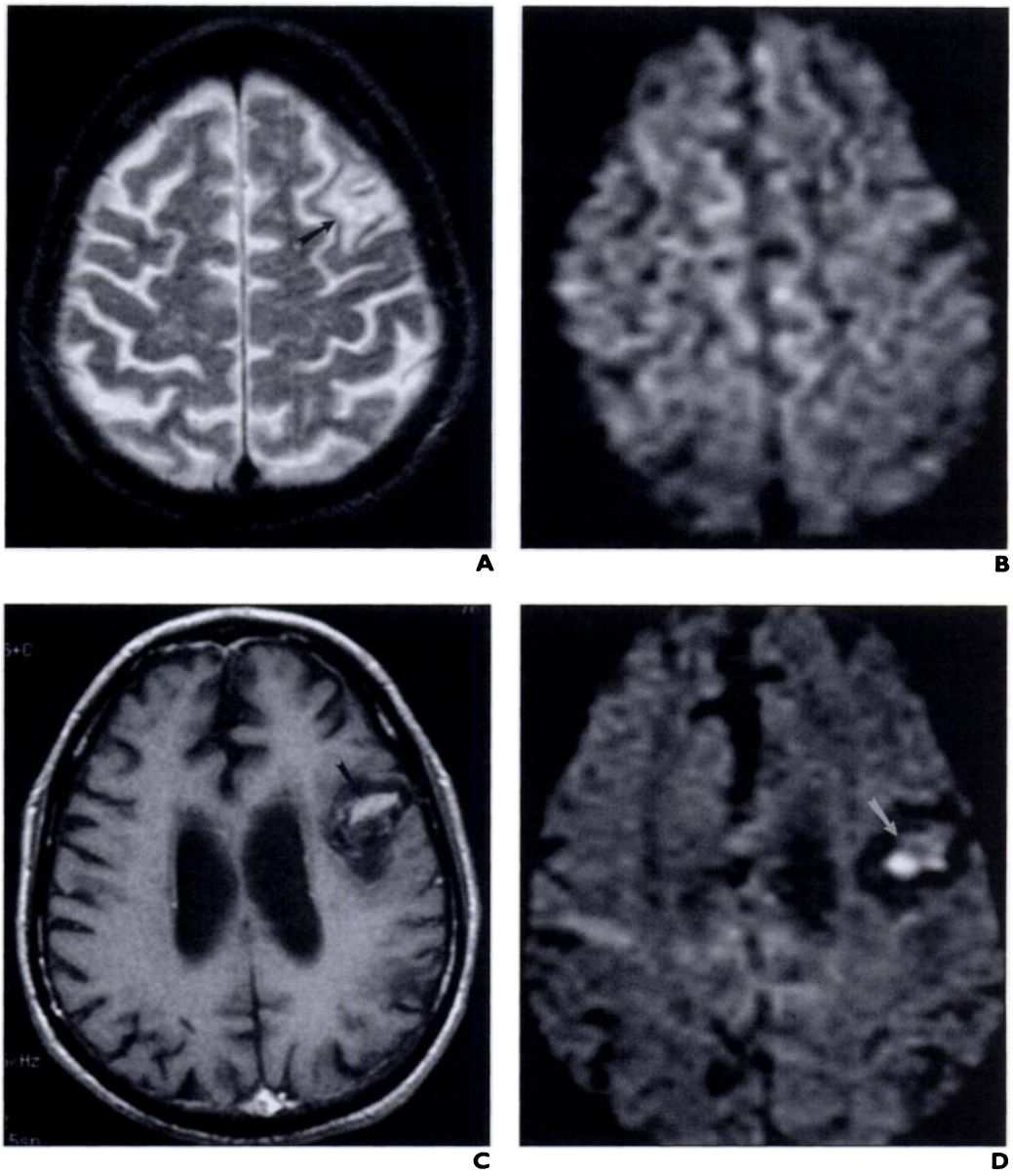


Fig. 3.—78-year-old man with hemorrhagic transformation of left frontal lobe ischemic infarction resulting in subcortical hematoma.
A, Axial T2-weighted MR image through high frontal region obtained 13 days after clinical ictus shows abnormally increased signal intensity (*arrow*) in region of infarct.
B, Axial diffusion-weighted MR image obtained at same time as **A** shows no signal abnormality in same region.
C, Axial T1-weighted MR image obtained at same time as **A** but located 2 cm inferior to A shows subacute hematoma with high-signal-intensity blood products centrally (*arrow*), consistent with methemoglobin formation.
D, Axial diffusion-weighted MR image obtained at same time as **C** shows focal area of hyperintensity within hematoma (*arrow*) that corresponds to high-signal-intensity area in **C**.

aging studies were interpreted as normal. Because of persistent symptoms, the patient was rescanned 24 hr later, at which time a left pontine infarct was clearly seen on diffusion-weighted, T2-weighted, and FLAIR images. Retrospective review of the first study revealed a subtle pontine diffusion abnormality that was not identified prospectively by either neuroradiologist. Presumably, it was overlooked initially because it was partially obscured by susceptibility artifacts at the central skull base. The second false-negative result was in an examination performed on day 1 in a patient who presented with diplopia and ophthalmoplegia. Because of these convincing clinical findings, a diagnosis of pontine infarct was made clinically, but no follow-up imaging was performed.

Finally, the presence of blood products creates an interesting and, to our knowledge, previously unreported problem for determining infarct age on diffusion-weighted images. The center of a subacute hematoma in one patient remained bright on diffusion-weighted images long after the nearby infarcted brain parenchyma returned to normal signal intensity (Fig. 3). Whether this finding was due to peculiar diffusion properties of the hematoma itself or resulted from T1 and T2 relaxation effects requires further investigation.

In conclusion, we found abnormal signal intensity to be present on diffusion-weighted studies in all acute stroke patients examined within 24 hr of symptom onset and in up to 94% of patients studied during the first 2 weeks after ictus. The percentage of abnormal findings declined over time, with no signal intensity abnormality seen on diffusion-weighted imaging performed on patients with infarctions more than 2 weeks old.

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