Diffusion-weighted Magnetic Resonance and Magnetization Transfer Imaging in the Assessment of Ischemic Human Stroke

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We compared characteristic features in ischemic stroke lesions from the hyperacute to the chronic stage on diffusion-weighted (DW) and magnetization transfer (MT) images with those on T2-weighted (T2W) images, and assessed changes in apparent diffusion coefficient (ADC), MT effect (MTe), and T2 ratios (infarct/normal) over time. DW images were particularly useful for detecting hyperacute infarcts within 6 hours of onset and in distinguishing acute lesions from chronic lesions. ADC ratios were lower within 7 days after onset and rose toward 1.0 in the subacute phase, becoming relatively isointense on ADC maps, but elevated thereafter. Although MTe ratios were unchanged or only subtly changed in the acute stage, they became significantly lower in the subacute and chronic stages. These combined magnetic resonance (MR) techniques were useful in the assessment of ischemic stroke and facilitated the determination of the age of cerebral infarct. (Internal Medicine 37: 360-365, 1998)

**Key words:** cerebral infarct, magnetic resonance (MR) imaging, apparent diffusion coefficient (ADC), magnetization transfer effect (MTe), T2-weighted (T2W) imaging

**Introduction**

Magnetic resonance (MR) imaging is widely used in the diagnosis of cerebral ischemia. However, conventional T1-weighted (T1W) and T2-weighted (T2W) imagings are not capable of reliably visualizing the lesion within the initial hours following ischemic stroke and often do not provide an accurate estimate of the age of infarct, which are very important findings when planning treatment strategy.

Diffusion-weighted (DW) imaging, which detects changes in the diffusion of water molecules associated with cytotoxic edema, has shown promise in early lesion localization. Recent studies in human stroke employing DW imaging have demonstrated early ischemic changes within 2 or 3 hours after ischemic stroke (1–3). Another new means to generate contrast with MR is magnetization transfer (MT) imaging (4). MT is based on interactions between the protons which are immobile or closely bound to macromolecules and free protons in tissue (5). Since there are progressive changes in the protein-bound water within the lesions as the infarct evolves, MT imaging may offer the potential to estimate the age of infarct (6).

In this study, we compared characteristic features in ischemic lesions from the hyperacute to the chronic stage on DW and MT imagings with those on T2W imagings and investigated whether these techniques can assist in determining the age of cerebral infarct.

**Subjects and Methods**

Twenty-one patients (13 men, 8 women) ranging in age from 46 to 88 years were studied one to three times (a total of 40 studies) at various intervals after the onset of symptoms attributable to focal cerebral ischemia. Only patients in whom an infarct was eventually confirmed by conventional computed tomography (CT) or T2W imagings were included. The precise time of stroke onset could be determined in all of the imaged ischemic lesions. Eleven lesions involved the cerebral cortex in the territory of the middle or posterior cerebral artery, and another ten lesions involved the basal ganglia, thalamus, corona radiata, and centrum semiovale. Patients with hemorrhagic infarct showing low signal intensity within an area of hyperintensity on T2W imaging or high signal intensity on
T1W imaging were excluded. The studies were grouped according to time periods after onset as follows: 0 to 24 hours (n=5; 2 hours, 6 hours, and 20 hours, 21 hours, and 23 hours), 1 to 7 days (n=7), 1 to 3 weeks (n=10), 3 weeks to 2 months (n=11), greater than 2 months (n=7).

All magnetic resonance imaging (MRI) studies were performed on a 1.5-Tesla whole-body imager (Magnex 150 HP; Shimadzu, Kyoto) with a transmit-receive head coil. T2W and T1W images in the axial plane parallel to the orbitomeatal line were obtained with a fast spin echo 4,000/110/2 and with a spin echo 500/15/2 (TR/TE/excitations) sequence, respectively. T2W images were obtained in all 21 patients (40 studies), and T1W images were obtained in 10 of 21 patients (14 studies). The section thickness was 8 mm with an intersection space of 2 mm. The matrix size was 256x179, and the field of view was 25 cm.

DW spin echo images were obtained by applying square diffusion-sensitive gradient pulses (gradient strength 10mT/m, duration 40 ms, separation 28 ms) on both sides of the 180° pulse with a 2–3 R-R interval (depending on cardiac gating)/140/1 (TR/TE/excitations). A baseline image with minimum diffusion weighting was obtained using a small b value (b=3 s/mm²). Diffusion-sensitized images were then obtained with the diffusion gradient in the phase-encoding (horizontal) direction, with a b value of 629 s/mm². We calculated apparent diffusion coefficient (ADC) values according to the following equation:

\[ \text{ADC} = \ln \left( \frac{S_1}{S_2} \right) / (b_2-b_1) \]

where S1 and S2 are the signal intensity of the baseline and DW images, respectively, and b1 and b2 are the b values for the corresponding pulse sequence.

MT imaging was performed by obtaining 2-dimensional gradient-echo 390/12/2 (TR/TE/excitations) sequence with a flip angle of 60°. The saturation pulse had the following parameters: off-resonance gaussian pulse centered 1.0 kHz below water frequency with a duration of 8.192 ms, a band width of 121.5 Hz and an irradiation pulse amplitude of 13 μ Tesla. The amount of MT was quantified by calculation of the MT effect (MTe) defined as (Mo–Ms)×100/Mo. Mo and Ms represent the signal intensity of an area with the saturation off and on, respectively. Section thickness, matrix size, and field of view on DW and MT imaging were the same as those used for T2W imaging. In both DW and MT imaging, six axial slices were obtained, including at the level of the ischemic lesions. ADC and MTe values were measured from a region of interest in the center of the area of ischemia and from a matching location in the uninvolved contralateral hemisphere. Intensity values on T2W imaging were also obtained from the same anatomic locations in the ischemic and contralateral hemisphere. T2, ADC, and MTe ratios for the infarct to normal hemisphere (infarct/normal) were computed.

T2W, and DW images were obtained in all 21 patients (40 studies), and MT images were obtained in 17 of 21 patients (32 studies).

Values were revealed as means±SD. The data were analyzed by a one-way analysis of variance (ANOVA) with time from stroke onset as the grouping factor and ratios of T2, ADC, and MTe as dependent measures. Differences in values between at 0 and 24 hours and at other times were compared by an ANOVA with Fisher’s PLSD. A p value of less than 0.05 was considered to be statistically significant.

Results

With DW imaging, acute infarct appeared as an area of hyperintensity compared to normal tissue and as an area of low signal intensity on ADC maps, indicating reduced ADC values. In 2 out of 5 patients studied within 24 hours (times; 2 hours, and 6 hours), only DW images detected the lesion, whereas T2W images showed no definite signal abnormalities (Fig. 1). Although the lesions were demonstrated as areas of hyperintensity on both DW and T2W images in patients studied at longer than 20 hours, acute infarcts could be readily distinguished from chronic infarcts on DW images. However, acute infarcts either could not be detected or showed relatively more subtle changes on MTe images. Therefore, DW imaging is the most sensitive technique for visualizing acute ischemic lesions, whereas MTe imaging is not as good as T2W imaging for the detection of acute infarct.

At the subacute stage, T2W image intensity transiently decreased, and thereafter increased. Changes on DW images appeared less intense, and lesions appeared relatively isointense on ADC maps, whereas lesions showed low signal intensity on MTe images (Fig. 2). MTe imaging was a more sensitive technique than DW and T2W in the evaluation of subacute infarct because of relatively less intensity on DW images and transiently decreased intensity on T2W images.

Although chronic infarcts were shown as areas of high signal intensity on T2W images, lesions could not be distinguished from acute infarcts. However, since ADC maps showed higher signal intensity and MTe images showed lower signal intensity, chronic infarcts were easily distinguished from acute or subacute lesions on these images.

Ratios of T2, ADC, and MTe at various time intervals after stroke are shown in Table 1. ANOVA revealed an overall effect with time with regard to ratios of T2 (F [35, 4] = 13.36; p<0.0001), ADC (F [35, 4] = 52.80; p<0.0001), and MTe (F [27, 4] = 16.36; p<0.0001). Figure 3 illustrates the comparison of chronological changes in T2, ADC, and MTe ratios. Two out of 5 patients studied within 24 hours had normal T2 ratios of around 1.0. The T2 ratio increased from 1 to 7 days, transiently decreased from 1 to 3 weeks, then rose over 2.0 thereafter. The ADC ratio was lowest at both 0 to 24 hours and 1 to 7 days after stroke, rose toward 1.0 at 1 to 3 weeks, and was markedly elevated at 3 weeks later after onset. On the contrary, the MTe ratio was unchanged at 0 to 24 hours, and gradually decreased thereafter, becoming significantly lower at 1 to 3 weeks and was markedly decreased at 3 weeks later.

Discussion

The present study demonstrated characteristic features of T2, DW, and MTe images at different intervals of the stroke, and ratios of T2, ADC, and MTe also showed characteristic
Figure 1. MRI about 6 hours (A–D), and 31 days (E–G) after the onset of cerebral ischemia (75-year-old, female). A) It is difficult to detect the signal intensity changes on T2W image. B) The DW image shows fresh ischemic lesions as areas of high signal intensity in the cortical gray matter of the left middle cerebral artery territory. C) The lesion appears as low signal intensity on the ADC map, indicating reduced ADC. D) The MTe image shows no signal abnormalities. E) The T2W image shows high signal intensity. F) The ADC map shows high signal intensity, indicating increased ADC. G) The MTe image shows low signal intensity.

values. These results indicate that the clinical utility of these MR techniques differs depending on the time period after stroke onset.

Early ischemic changes have been detected on DW images when T2W images are normal in both experimental (7, 8) and clinical (1–3) studies. DW imaging has been shown to be more sensitive than T2W imaging for detecting ischemia within several hours in human stroke, reflecting decreased ADC values (1–3). The initial decrease in ADC values is related to early pathophysiological changes including energy failure and cytotoxic edema. We confirmed the superiority of DW imaging for detecting hyperacute cerebral infarcts, as only DW images could depict early changes within 6 hours after onset. Moreover, these advantages indicate that DW imaging is useful in distinguishing acute from chronic infarcts in patients with multiple cerebral infarctions.

However, at the subacute stage, the changes on DW images were less intense as the rise in ADC ratio approached control values (ratio = 1). This represents an inevitable point in the transition of decreased ADC acutely to increased ADC chronically, but is not a true normalization of the tissue. During this period the intensity of infarct on T2W images decreases transiently. In some patients the appearance of lesions as isointense or slightly hyperintense is referred to as “MR fogging” (9). The exact mechanisms of this phenomenon remain unknown. Although patients with hemorrhagic infarction shown on T2W or T1W images were excluded from this study, the permeability of capillaries and arterioles in the infarcted lesion increases, and diapedic hemorrhage may occur. Moreover, scavenger activity is at its highest level, the infarcted area is loaded with lipid-laden macrophages during this period, and the water content of the lesion is close to that of the normal brain. Such factors may be responsible for the decreased intensity of lesions on T2W images (9). As subacute infarcts show a relatively low T2W signal and isointense ADC maps, T2W and DW imagings are not so useful in the assessment of infarct localization at the subacute stage. However, at the chronic stage T2 ratio increased again, and the ADC ratio was extremely elevated due to cell lysis and the ability of water to diffuse more freely in the infarct.

On the other hand, the infarcts at the subacute and chronic stages were shown as areas of low signal intensity on MTe images, although acute lesions were isointense. MTe was unchanged or slightly changed at the acute phase, and the ratio was significantly lower at the subacute and chronic phases. MT is based on the interaction between populations of mobile protons and restricted protein-bound protons within tissues (5). This effect is greatest in tissues having a high protein to water ratio and smallest in tissues having a low protein to water ratio. Histopathologically, at the acute phase neurons show ischemic degeneration and eventual dissolution with infiltration of polymorphonuclear cells within lesions (10). During this period there are relatively normal amounts of protein-bound water which remain, as no significant decrease of MTe ratio is shown. As the infarct evolves, liquefaction begins with removal of debris by increased numbers of macrophages, and the result of fluid accumulation is increased infarct volume. This results in

Table 1. T2, ADC, and MTe Ratios at Various Time Intervals after Stroke Onset

<table>
<thead>
<tr>
<th>Time after onset</th>
<th>T2 ratio</th>
<th>ADC ratio</th>
<th>MTe ratio</th>
</tr>
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<tbody>
<tr>
<td>0–24h</td>
<td>1.38 ± 0.37 (5)</td>
<td>0.44 ± 0.12 (5)</td>
<td>0.98 ± 0.01 (3)</td>
</tr>
<tr>
<td>1–7d</td>
<td>1.91 ± 0.20** (7)</td>
<td>0.59 ± 0.13 (7)</td>
<td>0.91 ± 0.03 (4)</td>
</tr>
<tr>
<td>1–3w</td>
<td>1.61 ± 0.30 (10)</td>
<td>0.91 ± 0.16** (10)</td>
<td>0.85 ± 0.09* (9)</td>
</tr>
<tr>
<td>3w–2m</td>
<td>2.21 ± 0.29*** (11)</td>
<td>1.56 ± 0.37*** (11)</td>
<td>0.70 ± 0.11*** (11)</td>
</tr>
<tr>
<td>2m&lt;</td>
<td>2.48 ± 0.43*** (7)</td>
<td>2.03 ± 0.23*** (7)</td>
<td>0.56 ± 0.10*** (5)</td>
</tr>
</tbody>
</table>

ADC: apparent diffusion coefficient, MTe: magnetization transfer effect, h: hours, d: days, w: weeks, m: months, ( ): number of patients. *p<0.05, **p<0.01, ***p<0.0001 as compared with values at 0–24h.
Figure 2. MRI 17 days after the onset of cerebral ischemia (74-year-old, female). A) The T2W image shows lesions as high signal intensity in the left corona radiata and temporal white matter. B) The ADC map shows iso- to high signal intensity, indicating slightly increased ADC. C) The MTe image shows definite low signal intensity.

the development of a decreased MTe ratio at the subacute phase. At the chronic stage, cavitation of the tissue becomes evident, and eventually a fluid-filled cavity develops, resulting in a markedly decreased MTe ratio due to the presence of more mobile or free protons within tissues. Therefore, the chronological course of changes in the MTe ratio, in addition to changes of the ADC ratio, correlates with the morphologic evolution of infarct. Serial changes in MTe ratio are reciprocal to those in ADC ratios because the amount of MT, which depends on the number of protons that are immobile or closely bound to macromolecules, is likely to reflect the diffusivity of water.

In this study, we analyzed the ratios of ADC and MTe at various time periods after stroke onset, but not absolute values, because values of ADC and MTe have been shown to differ in various areas of the brain. ADC values greatly vary, depending on fiber orientations in the white matter due to diffusion anisotropy. MTe values in the white matter are higher than those in the gray matter because of the presence of macromolecular components such as myelin (11). Ratio changes reflect differences of visual contrast on MR images, and it is clinically more practical to use ratios in MR parameters rather than absolute values.

In conclusion, considering the advantages and disadvan-
Figure 3. A comparison of the chronological course of changes in the T2, ADC, and MTe ratios. Bars indicate mean values. ADC: apparent diffusion coefficient, MTe: magnetization transfer effect, h: hours, d: days, w: weeks, m: months.

Advantages of MR techniques at various stages after stroke onset, combined studies of such techniques are useful in the evaluation of cerebral infarction and can assist in determining the time after infarct onset.

Acknowledgements: We wish to thank Mr. K. Shimizu and other engineers of the Department of Medical Applications of the Shimadzu Corporation for their support and technical assistance. We are also grateful to Prof. J. P. Barron of the International Medical Communications Center for his review of the manuscript.

References