Longitudinal Changes in Proton Magnetic Resonance Spectroscopy in Cerebral Infarction

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**Background and Purpose:** Proton magnetic resonance spectroscopy has revealed changes in lactate and N-acetyl-aspartate in acute cerebral infarction. However, the details of these drastic changes and subsequent chronic changes have not been clarified. The purpose of this study was to disclose longitudinal changes in spectra seen in proton magnetic resonance spectroscopy.

**Methods:** Six patients with completed cerebral infarction were examined longitudinally with localized proton magnetic resonance spectroscopy.

**Results:** (1) In the acute stage (within 2 days after onset), two drastic changes were observed: N-acetyl-aspartate decreased rapidly and severely within 2 days after onset, and lactate increased immediately and reached a high level in the acute stage after onset. (2) In the chronic stage (more than 1 month after onset), two features were observed: lactate, which had increased in the acute stage, remained high for more than 1 month, and other signals such as those of N-acetyl-aspartate, choline, and phosphocreatine/creatine decreased dramatically.

**Conclusions:** These results suggest that N-acetyl-aspartate and lactate as revealed by proton magnetic resonance spectroscopy can be useful indicators of the ischemic damage to the brain in clinical cases of cerebral infarction. (Stroke. 1993;24:1316-1321.)

**Key Words** • cerebral infarction • lactates • spectroscopy, nuclear magnetic resonance

Recent in vivo studies using phosphorus-31 (^31P) nuclear magnetic resonance spectroscopy (MRS) and proton MRS (^1H-MRS) have clearly documented metabolic changes in experimental animals. After the onset of cerebral ischemia, deterioration of the energy state, accumulation of lactate, and coincident lactic acidosis are observed. Additionally, a sophisticated clinical application of MRS with a newly developed signal localization technique has opened the door to the noninvasive clinical examination of cerebral metabolism. Subsequently, some interesting facts such as an acute increase in lactate and decrease in N-acetyl-aspartate (NAA) were reported. However, few systematic studies have been done in clinical cases of cerebral infarction. Particularly, longitudinal changes in the decreased NAA and accumulated lactate in the infarcted brain have not been fully investigated. Accordingly, the aim of this study was to reveal longitudinal changes in cerebral metabolism after ischemic insult in clinical cases using ^1H-MRS.

**Subjects and Methods**

**Methods**

Magnetic resonance imaging (MRI) and MRS were performed with a whole-body 1.5 T MRI system (Magnetom SP, Siemens, Erlangen, Germany) using a head coil. Localized ^1H-MRS was achieved by stimulated echo acquisition mode. The suppression of the water proton signal was accomplished by preceding chemical shift selective radio frequency pulse to water proton. T2-weighted transverse images and T1-weighted coronal or sagittal images or both were taken to place the volume of interest (VOI). The VOI (3×3×3 cm, 27 cm³) was precisely localized centrally to the infarcted brain using two or three images (transverse and sagittal/coronal). To avoid equivocal signal contamination from normal (nonischemic) tissue, we selected for this study patients who had a large infarcted area (major stroke) on MRI. Therefore, the VOI was placed within the infarcted area, and signal contamination from normal tissue was minimized. The echo and repetition times used in the present study were 270 and 1500 milliseconds, respectively. The total acquisition number was 500 scans. The total examination was completed in less than 45 minutes (imaging time, 15 minutes; preparation time for spectroscopy, 10 minutes; spectra acquisition time, 10 minutes). We did not demand a perfect shimming condition in clinical cases, especially in patients with cerebral stroke in the acute stage, so that the total examination time could be shortened as much as possible. Consequently, the time for the shimming procedure was limited to 5 minutes or less. In most cases, however, the half-width of the water proton peak, which reflects the degree of shimming, was less than 7 Hz, small enough for clinical evaluation of the acquired spectra. The spin-echo time was set at 270 milliseconds, to provide in-phase conditions for the lactate methyl group
doublet (spin-spin coupling constant $[J]=7.35$ Hz). When a typical doublet peak of lactate was recognized, all other signals were assigned using the chemical shift of lactate (1.33 ppm). In the chronic stage of infarction, which had a poor signal-to-noise ratio, the chemical shift of the residual water proton signal (4.7 ppm) was used as a reference to assign other low signals.

In our study, the longitudinal changes in the peak areas of NAA and lactate were analyzed. For this purpose, the control for these peak areas was obtained from the NAA peak on the contralateral side of the infarction. The ratio of the peak area of these two signals to the peak area of NAA on the contralateral side was calculated. Although 12 patients were exam-

### Table 1. Clinical Summary of Six Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Occluded artery</th>
<th>Outcome (ADL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>M</td>
<td>T</td>
<td>MCA</td>
<td>Dead (pneumonia)</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>F</td>
<td>E</td>
<td>ICA</td>
<td>Dead (brain herniation)</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>M</td>
<td>E</td>
<td>MCA</td>
<td>Disabled</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>T</td>
<td>PCA</td>
<td>Self-care</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>E</td>
<td>MCA</td>
<td>Self-care</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>F</td>
<td>T</td>
<td>ICA</td>
<td>Disabled</td>
</tr>
</tbody>
</table>

ADL, activities of daily living; T, thrombosis; MCA, middle cerebral artery; E, embolism; ICA, internal carotid artery; PCA, posterior cerebral artery. Differential diagnosis of cerebral thrombosis and embolism was performed based on clinical course and angiographic findings.

In Fig 1. Top: T2-weighted magnetic resonance image shows volume of interest as a square. Bottom left: Normal proton magnetic resonance spectroscopic ($^1$H-MRS) pattern of the contralateral side of the infarcted brain. Three prominent signals are choline (Cho), phosphocreatine and creatine (PCr/Cr), and N-acetyl-aspartate (NAA). Bottom right: Typical $^1$H-MRS pattern of cerebral infarction 24 hours after onset in the left temporal lobe. Huge peak of lactate is seen, and NAA is severely decreased.
ined, consecutive examinations in the acute stage (more than two measurements within 48 hours) were done on six patients.

Patients

From April 1991 to September 1991, six patients with cerebral infarction were examined. The patients had an infarcted area on MRI large enough to be covered by the VOI of $1^H$-MRS ($3 \times 3 \times 3$ cm) (Fig 1). Patients with obvious hemorrhagic infarction revealed by computed tomography were not included in this study. Conventional angiography was performed in four patients, and the occlusion of the responsible artery was revealed. However, angiography was not repeated, so information about the recanalization of the occluded artery (recirculation of the infarcted brain) was not obtained. The Table summarizes the clinical details of these six patients. Patients were examined longitudinally from the acute stage (within 2 days after the onset of ischemic insult) to the chronic stage (more than 1 month after onset). In most cases, $1^H$-MRS was performed every 1 to 2 weeks after stroke onset.

Results

$1^H$-MRS Pattern in Acute Stage of Cerebral Infarction

Fig 1 shows a normal pattern of $1^H$-MRS of predominantly cerebral white matter (Fig 1, bottom left) and a typical pattern of the infarcted brain in the acute stage (Fig 1, bottom right). In normal $1^H$-MRS, three prominent signals were consistently detected: choline, phosphocreatine/creatine, and NAA. In the spectrum for the infarcted brain, in contrast, two major changes were observed: a decrease in NAA in the infarcted brain—namely, NAA, which is normally the most prominent signal, was lower than on the contralateral side—and an increase in the lactate signal.

Longitudinal changes in the peak areas of NAA and lactate in the acute stage are shown in Fig 2. The decrease in NAA appeared within hours after the onset of ischemia, and NAA was almost lost within 2 days. The increase in lactate also started immediately after stroke onset and seemed to reach a high level within several days. Fig 3 shows representative cases.

MRS Pattern in Chronic Cerebral Infarction

Fig 4 shows typical longitudinal changes in lactate in cerebral infarction in the chronic stage. Because NAA almost disappeared in the chronic stage (48 hours after onset), its change is not shown. The elevated lactate remained at a constant high level for more than 1 month. A small amount of lactate was detected even in the chronic stage. In most cases (Fig 5, top), NAA decreased rapidly in the acute stage, and its signal became depressed below the noise level in the chronic stage. In one case (Fig 5, bottom), NAA did not disappear completely but remained even in chronic infarcted brain. Other signals (choline and phosphocreatine/creatine) remained longer than NAA, although they decreased gradually and became depressed below the noise level in the chronic stage. The choline signal was likely to remain longer than other signals. But consequently, the spectrum in chronic infarction showed a severely decreased signal-to-noise ratio in most cases.

Discussion

Quantitative analysis using MRS is still controversial, especially in clinical MRS. The signal intensity observed in MRS is a multifactorial function. It is related to the condition of the measurement and relaxation time of each metabolite and “visibility” by nuclear magnetic resonance as well as the concentration of the metabolite. The absolute quantity can hardly be measured with this technique in clinical patients. However, under the same measurement parameters (repetition time and echo time), clinical $1^H$-MRS is relatively reproducible. The signal height is dependent on $T_2^*$ time (practical transverse relaxation time ruled by true $T_2$ time and inhomogeneity of static magnetic field), but the peak area is not seriously dominated by the $T_2^*$ time (different shimming condition). Therefore, in our study, longitudinal changes in the peak areas of NAA and
lactate were analyzed (Figs 2 and 4) using peak area ratio. For comparison among different patients, some control is necessary. For this purpose, relative analysis using cholines or phosphocreatine/creatine has been performed in other studies.\textsuperscript{12-14} However, even cholines and phosphocreatine/creatine show substantial changes after ischemic insult. Therefore, in this study, the control for these peak areas was obtained from the NAA peak of the contralateral side of the infarction.

As described by Bruhn et al.,\textsuperscript{9} \textsuperscript{1}H-MRS demonstrates a change after an ischemic insult in clinical cases. Their study revealed an increase in lactate and decreases in NAA and phosphocreatine/creatine in the acute stages after cerebral infarction. We have shown a persistent lactate increase in completed infarction in rats using an experimental ischemic model.\textsuperscript{3} However, longitudinal changes in NAA and lactate in clinical cases have not been fully investigated.\textsuperscript{10,11}

The decrease in NAA occurred rapidly in the acute stage of cerebral infarction, and this change appeared to be irreversible. NAA is considered to be a neuron-specific amino acid.\textsuperscript{15,16} The decrease in NAA is considered to indicate irreversible neuronal damage in the infarcted brain. However, the degree of NAA decrease is not uniform. In some cases, it was rapid and severe, and no NAA was observed in the chronic stage after stroke. In other cases, the NAA decrease was minor, and NAA was observed even in the chronic stages. The variations in the peak areas of NAA and lactate could be due to different positioning of the VOI at different observations and different MRI parameters and settings. To eliminate this problem, we placed the VOI at the center of the infarction large enough for a $3\times3\times3$ cm VOI and used the same MRI parameters. Accordingly, the extent of the neuronal damage appeared

**FIG 3.** Spectra show typical change of pattern of proton magnetic resonance spectroscopy in acute stage of infarction in two cases. Top: Eight hours after infarction onset, N-acetyl-aspartate (NAA) decreased but still can be observed; elevated lactate reached its plateau level. Twenty-four hours after onset, NAA completely disappeared, and elevated lactate stayed at the same level. This patient (case 2) died 7 days after onset due to brain herniation. Bottom: Same changes are seen in case 3. Cho, choline; PCr, phosphocreatine; Cr, creatine.
FIG 4. Plot shows longitudinal changes in lactate (Lac) in the chronic stage. NAA, N-acetyl-aspartate.

Sequential Follow-up

Day 1  1 Week  3 Weeks  5 Weeks

Lactate  Lactate  Lactate  Lactate

Sequential Follow-up

Day 1  1 Week  3 Weeks  5 Weeks

Lactate  Lactate  Lactate  Lactate

FIG 5. Proton magnetic resonance spectroscopy spectra show sequential follow-up of lactate in the chronic stage. Top: N-acetyl-aspartate (NAA) disappeared in acute stage. Increased lactate persists for more than 3 weeks. All signals except for small peak of persistent lactate disappeared in 5 weeks. Bottom: NAA decreased in acute stage but did not disappear completely. Increased lactate persisted more than several weeks and then declined gradually.
tovary, even if the MRI indicated similar morphological changes caused by infarction.

Lactate generated in the ischemic brain remained for a long time. Plausible interpretations of this persistent high lactate level are (1) lactate is produced consistently even in the subacute and chronic stages; (2) lactate produced in the acute stage remains in the damaged tissue, where no significant blood flow exists and lactate cannot be washed out; (3) lactate is produced in the ischemic penumbra around the core of infarction; and (4) lactate is produced by phagocytic cells infiltrating the brain parenchyma after a stroke, referred to by Graham et al.10 We have demonstrated in an experimental ischemic study in rats17 that the second possibility, “retention” of lactate produced in the acute stage, is likely. In clinical cases, however, recanalization of the occluded artery or development of collateral circulation frequently occurs. This may replenish glucose supply to the damaged tissue. An inadequate supply of glucose to damaged tissue may be responsible for the persistent lactate. Rothman et al18 have suggested from a study of one clinical case that lactate is consistently produced even in chronic infarcted brain.

In chronic infarction, spectra with very poor signal-to-noise ratios were observed, distinctive from the 31P-MRS pattern of chronic infarction. As shown by Bottomley et al.,19 31P-MRS in chronic infarction reveals the pattern of normal brain except for a general decrease in each signal. Our experimental study with the rat model indicated that this pattern of 31P-MRS spectra in chronic infarction reflected reactive gliosis in the lesion.20 In other words, normal brain tissue and reactive gliosis have a similar pattern of metabolic changes in terms of high-energy phosphates. As far as NAA, choline, and lactate observed by 1H-MRS are concerned, reactive gliosis and normal brain tissue have a quite different pattern. It is conceivable that the ischemic penumbra has a condition with an “intermediate” 1H-MRS pattern between normal brain and chronic infarcted brain. At present, the spatial resolution of clinical 1H-MRS is insufficient to reveal the metabolism of small regions such as the ischemic penumbra.

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