Longitudinal Changes of Metabolites in Frontal Lobes After Hemorrhagic Stroke of Basal Ganglia
A Proton Magnetic Resonance Spectroscopy Study

Masahito Kobayashi, MD, PhD; Hideichi Takayama, MD, PhD; Sadao Suga, MD, PhD; Ban Mihara, MD, PhD

Background and Purpose—We investigated serial metabolic changes in frontal lobes of patients with deep intracerebral hemorrhage (ICH) to examine the correlation between N-acetylaspartate (NAA) and degree of motor impairment or clinical outcome.

Methods—Twenty patients with deep ICH were examined with proton magnetic resonance spectroscopy with the application of a multivoxel method (1 voxel = 10 × 10 × 20 mm; 64 voxels). NAA/creatine ratios in the white matter of the primary motor and premotor areas on both sides were measured sequentially: within 48 hours, at 2 weeks, and 1 month after onset. The National Institutes of Health Stroke Scale and Barthel Index for disability were measured for each patient.

Results—In the primary motor area on the affected side, where the hematoma did not extend, the NAA/creatine ratio decreased sequentially. At 48 hours and 2 weeks after onset, a negative correlation was detected between NAA/creatine and hematoma volume, but there was no correlation 1 month later. At 2 weeks, NAA/creatine correlated negatively with motor impairment (r = −0.750), and there was a significant correlation with clinical outcome as early as 2 weeks after onset (r = 0.954). These sequential changes of NAA/creatine varied according to patients’ long-term clinical outcome. Patients with poor outcome demonstrated notable reduction of NAA/creatine over the bilateral frontal lobes.

Conclusions—The delayed gradual reduction of NAA/creatine ratio in the frontal lobes correlates with motor deficit and clinical outcome after deep ICH, suggesting that the neural networks in the frontal lobe could be important for recovery. (Stroke. 2001;32:2237-2245.)

Key Words: cerebral metabolism ■ intracerebral hemorrhage ■ recovery of function ■ spectroscopy, nuclear magnetic resonance

Hemorrhagic stroke accounts for approximately 10% of all stroke, which is a common cause of death and also one of the most prominent causes of severe disability in adults.1 The poor outcomes after intracerebral hemorrhage (ICH) may be associated with various factors, such as hemorrhage volume and extension, age, increased intracranial pressure, herniation of brain tissue, or possible presence of secondary neural injury that would develop over a period of hours or days after hemorrhagic stroke.2-7 It has been reported that clinical outcomes after deep ICH correlate with reduction of cerebral blood flow in bilateral frontal lobes.8,9 Cerebral ischemia is postulated to be one of the mechanisms of neural injury in the early periods after experimental ICH,10-12 but this is still controversial.13

As for functional recovery after stroke, previous studies have indicated some possible role of premotor and somatosensory motor areas and unaffected frontal lobes,14-17 but the role of these areas is subject to controversy.18 Among hemorrhagic stroke, deep-seated ICHs are encountered most commonly and affect the striatocapsular area, which would lead to motor impairment.19 Karibe et al21 have indicated that diffusion-weighted MRI can evaluate corticospinal tract injury and provide predictive value of motor function after deep ICH. The subcortical structures of frontal lobes have been suggested to be important for improvement of functional outcome after hemorrhagic stroke.22 In our study we focused on cerebral metabolism, which may reflect the function of the corticospinal tract or other subcortical architecture, such as basal ganglia circuits in the frontal lobe.23

Proton MR spectroscopy (MRS) is a noninvasive instrument that assesses neural viability. Reduction of N-acetylaspartate (NAA) is proposed to indicate an irreversible loss of viable
TABLE 1. Patient Clinical Data and Hematoma Characterization

<table>
<thead>
<tr>
<th>Age, y/Sex</th>
<th>Affected Side</th>
<th>Location</th>
<th>Hematoma Volume, mL</th>
<th>Surgery/Date of Surgery</th>
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</thead>
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<tr>
<td>58/F</td>
<td>R</td>
<td>Thalamus</td>
<td>11</td>
<td>No</td>
</tr>
<tr>
<td>60/M</td>
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<td>Thalamus</td>
<td>4</td>
<td>VD/1 d</td>
</tr>
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<td>Thalamus</td>
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</tr>
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<td>R</td>
<td>Putamen</td>
<td>23</td>
<td>Aspiration*/0 d</td>
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<td>R</td>
<td>Putamen</td>
<td>42</td>
<td>Aspiration*/3 d</td>
</tr>
<tr>
<td>74/M</td>
<td>R</td>
<td>Putamen</td>
<td>70</td>
<td>Aspiration*/4 d</td>
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<td>R</td>
<td>Putamen</td>
<td>20</td>
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<td>R</td>
<td>Putamen</td>
<td>5</td>
<td>No</td>
</tr>
<tr>
<td>49/F</td>
<td>L</td>
<td>Thalamus</td>
<td>4</td>
<td>No</td>
</tr>
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<td>62/M</td>
<td>L</td>
<td>Thalamus</td>
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<td>Putamen</td>
<td>8</td>
<td>No</td>
</tr>
<tr>
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<td>No</td>
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<tr>
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<td>L</td>
<td>Putamen</td>
<td>23</td>
<td>Aspiration*/3 d</td>
</tr>
<tr>
<td>63/F</td>
<td>L</td>
<td>Putamen</td>
<td>20</td>
<td>Aspiration*/4 d</td>
</tr>
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<td>Putamen</td>
<td>50</td>
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<tr>
<td>81/M</td>
<td>L</td>
<td>Putamen</td>
<td>70</td>
<td>Aspiration*/4 d</td>
</tr>
</tbody>
</table>

R indicates right; L, left; and VD, ventricular drainage.
†Craniotomy with evacuation of hematoma.
*Stereotaxic aspiration of hematoma.

neurons but also can be found in disorders in which neuronal damage or dysfunction is sublethal and reversible. Several studies have used this method and investigated the areas of both ischemic and hemorrhagic strokes at various time points. In this study we selected voxels located in the white matter of the premotor cortex and primary motor cortex on both sides to measure NAA in the affected hemisphere. Two observers confirmed symmetrical placement of the voxels on the frontal lobes of both sides. The voxel size was chosen to be large enough to include the white matter of the premotor and primary motor areas on both hemispheres, above the lateral ventricle, without involving the hematoma. Two observers confirmed symmetrical placement of the voxels on the frontal lobes of both sides. The voxel size was chosen to be large enough to include the white matter of the premotor and primary motor areas on both hemispheres, above the lateral ventricle, without involving the hematoma.

Subjects and Methods

Patient Population

This study included 20 patients, 11 men and 9 women (aged 49 to 81 years; mean age, 64.8 ± 9.0 years), with their first nontraumatic deep ICH who were hospitalized in Mihara Memorial Hospital within 48 hours after onset. All patients exhibited various degrees of hemiparesis caused by single unilateral ICH located in the basal ganglia and/or thalamus. The diagnosis of ICH was based on CT scans obtained immediately after arrival at the hospital. Patients were excluded if they had any contraindication to MRI or an ICH due to bleeding from tumor lesion, ruptured cerebral aneurysm, or hemorrhagic infarction. Table 1 shows the clinical details of the patients. The ICH volume was calculated as 1/2×long diameter×short diameter×thickness of the high-density area on CT scan.

Patients were treated surgically when they had ICH >40 mL. ICH >20 mL with disturbance of consciousness worse than stupor, or intraventricular extension of hematoma causing acute obstruction of the third ventricular outlet. Ten patients underwent surgery, and another 10 patients were treated medically. A craniotomy with evacuation of the hematoma was performed for 1 patient, stereotaxic aspiration for 8 patients, and ventricular drainage for 1 patient with acute hydrocephalus. All patients gave informed consent to the protocol, which was approved by the Human Rights Committee of the Institute of Brain and Blood Vessels.

MRI and MRS

All studies were performed with a standard circularly polarized head coil on a clinical 1.5-T whole-body MR system (Magnetom Vision, Siemens). We positioned patients in their natural supine posture and their heads in the head coil so that they were comfortable; foam pads were used to maintain their heads in as uniform a position as possible for serial studies. T1-weighted sagittal, coronal, and axial images were obtained to visualize the hematoma and motor cortices and to position the volume of interest for proton MRS (Figure 1). For the MRS study, we used a chemical shift spectroscopic imaging (CSI) sequence that used a point-resolved spectroscopy sequence (PRESS). A rectangular volume of interest of 80×80 mm and 20-mm thickness was positioned to include the white matter of the premotor and primary motor areas on both hemispheres, above the lateral ventricle, without involving the hematoma. Two observers confirmed symmetrical placement of the voxels on the frontal lobes of both sides. The voxel size was chosen to be large enough to include the white matter of the premotor and primary motor areas on both hemispheres, above the lateral ventricle, without involving the hematoma.

The intention of this study was to perform MRS serially at 3 time points: within 48 hours, at 2 weeks, and at 1 month after onset. However, some of patients could not complete this protocol in the acute stages because they could not enter the MRI and MRS examinations were performed in 9 patients, examinations were performed 2 weeks and 1 month later in 4 patients, and examinations were performed only 1 month later in 7 patients.
Assessment of Motor Impairment and Outcome

Motor function in the upper and lower extremities was assessed within 48 hours, at 2 weeks, and at 1 month after stroke, on the same day as the MRS examination, with a modified version of the National Institutes of Health (NIH) Stroke Scale (Table 2). We applied the sum of the arm and leg impairment scores for assessment of motor impairment. Clinical outcome was evaluated 2 months after stroke with the Barthel Index for disability. All patients were examined and followed up by a neurologist or a neurosurgeon who were blind to the imaging results.

Statistical Analysis

Spearman’s rank-order correlation coefficient was applied to detect the correlation between NAA/creatine and NIH Stroke Scale and between NAA/creatine and Barthel Index. Pearson’s correlation coefficient was applied for NAA/creatine and hematoma volume. Paired t test was used for comparison between data of NAA/creatine ratios obtained from affected and unaffected sides, and the Mann-Whitney test was used for data from different patient groups. ANOVA with repeated measures was applied to assess the serial changes of NAA/creatine and their variation among patients with different clinical outcomes. If ANOVA showed a significant effect of time points or a significant interaction among the patient groups, post hoc planned comparisons (Newman-Keuls test) were applied to identify the source of difference. The results were reported as mean±SD. Differences were considered significant at values of P<0.05.

Results

Comparison of NAA/Creatine Ratios Between Affected and Unaffected Sides

Figure 2A and 2B shows the NAA/creatine ratios in the white matter of the premotor and primary motor areas at each time point. Within 48 hours after onset, there was no significant difference between NAA/creatine ratios on the affected and unaffected sides. Two weeks after onset, NAA/creatine ratios were significantly lower on the affected side than on the unaffected side in the primary motor area (P<0.05). One month after onset, a significant difference was also detected in both the primary motor and the premotor areas (P<0.005). These results indicate the decrease of NAA/creatine ratio in the voxels of the frontal lobe, where the hematoma had not extended.

The data of the 9 patients who underwent MR studies at the 3 time points are summarized in Figure 2C, demonstrating the sequential changes of NAA/creatine ratios in bilateral primary motor areas. The serial data disclosed the sequential reduction of the NAA/creatine ratios in the primary motor area on the affected side >1 month after onset (F2,16=4.23, P<0.05), whereas those on the unaffected side did not show any significant longitudinal change. There was no statistically significant serial change in the premotor area (data not shown).

Hematoma Volume and NAA/Creatine Ratio

Figure 3 shows the correlation between hematoma volume and NAA/creatine ratio in the white matter of the primary motor area on the affected side. Within 48 hours and at 2 weeks after stroke, NAA/creatine correlates significantly with

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Table 2. Modified NIH Stroke Scale

<table>
<thead>
<tr>
<th>Motor Arm and Leg</th>
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<tbody>
<tr>
<td>0 = No drift</td>
</tr>
<tr>
<td>1 = Drift</td>
</tr>
<tr>
<td>2 = Some effort against gravity</td>
</tr>
<tr>
<td>3 = No effort against gravity</td>
</tr>
<tr>
<td>4 = No movement</td>
</tr>
</tbody>
</table>
hematoma volume \( r = -0.862, P < 0.005 \) and \( r = -0.774, P < 0.005 \), respectively), but at 1 month there was no significant correlation. NAA/creatinine decreased severely in some patients with even small-volume hematoma at 1 month. No correlation was detected between hematoma volume and NAA/creatinine in bilateral premotor areas and motor area on the unaffected side (data not shown).

Motor Impairment, Clinical Outcome, and NAA/Creatine Ratios in Primary Motor Area on Affected Side
Figure 4 indicates the relationship between the degree of motor deficit and NAA/creatinine in the primary motor area on the affected side. Within 48 hours, there was no correlation between NIH Stroke Scale score and NAA/creatinine ratio. There were significant correlations between them 2 weeks and 1 month after stroke \( (r = -0.750, P < 0.01 \) and \( r = -0.806, P < 0.001 \), respectively).

Figure 5 indicates the correlation between NAA/creatinine in the primary motor area and Barthel Index score 2 months after onset. In the acute stage after stroke, no significant correlation was detected between long-term clinical outcomes and either motor or premotor area. At 2 weeks and at 1 month after stroke, however, the severity of clinical outcome was closely correlated with NAA/creatinine ratios in the primary motor area \( (r = 0.954, P < 0.001 \) and \( r = 0.865, P < 0.0005 \), respectively).

Serial NAA/Creatine Change in Primary Motor Area and Variation According to Barthel Index
We evaluated the difference of these serial NAA/creatinine changes among patients who showed different clinical outcomes. The patients were divided into 3 subgroups according to their Barthel Index scores: 0 to 40, poor outcome; 45 to 70, moderate outcome; and 75 to 100, good outcome. Data of subgroups are shown in Figure 6. There were significant differences among the data at each time point \( (F_{2,12} = 14.77, P < 0.001 \) and among the subgroups partitioned by Barthel Index scores \( (F_{2,6} = 8.73, P < 0.05 \). A significant interaction was also demonstrated between the time course and subgroups \( (F_{4,12} = 7.43, P < 0.05 \). In the patients who showed good outcome, the NAA/creatinine ratio remained almost constant, whereas patients with moderate and poor outcome showed a significant decrease at 2 weeks after stroke. One month after stroke, the NAA/creatinine ratio of the moderate outcome subgroup increased to be significantly larger than that of the poor outcome subgroup, in which NAA/creatinine decreased further.

Motor Impairment, Clinical Outcome, and NAA/Creatine Ratios in Premotor Area and Primary Motor Area on Unaffected Side
NAA/creatinine ratios in both premotor and unaffected primary motor areas were also estimated to detect correlation with clinical outcome. There was no correlation between motor
impairment and NAA/creatine ratios in those areas at any time (data not shown). The clinical outcomes were not correlated with NAA/creatine ratios within either 48 hours or 2 weeks after onset. One month after stroke, however, a significant correlation was detected between clinical outcome and NAA/creatine ratios in all these areas (Figure 7). As shown, NAA/creatine ratios were especially low in patients who had poor Barthel Index scores (those in so-called persistent vegetative states).

**NAA/Creatine Ratio in Patients With Surgery**

The effect of surgery on the NAA/creatine ratios was also evaluated. Data are indicated as mean±SD. There was no statistical difference in age between patient groups with and without surgery (66.7±9.8 and 63.7±9.4 years, respectively). At onset, the mean hematoma volume in patients with surgery (40.1±24.0 mL) was significantly larger than that of those without surgery (11.4±10.5 mL; P<0.005), and there was a significant difference in NIH Stroke Scale score between the groups with and without surgery (7.6±0.7 and 4.8±2.5, respectively; P<0.005). The Barthel Index scores of patients with surgery (31.5±35.5) were significantly lower than those without surgery (69.5±34.1; P<0.05). However, we did not find a statistically significant difference in NAA/creatine ratios between groups with and without surgery (1.83±0.33 and 1.99±0.26, respectively).

**Discussion**

MRS allows the noninvasive assessment of cerebral metabolism and has been used for clinical studies on stroke, degenerative disease, and brain injury. NAA is one of the chemical substances in neuron cell bodies, dendrites, and axons, whereas creatine, which is in fact the sum of creatine and phosphocreatine, is found in neurons and glial cells. NAA is thought to reflect neuronal loss or dysfunction of neural activity, and NAA/creatine ratio has often been used for studies on stroke patients, with creatine applied as an internal standard for normalization of signal intensities. The NAA/creatine ratio should be used in regions where creatine remains constant because a change in glial metabolism could influence the NAA/creatine ratio. Other techniques exist, such as normalization to the internal water for absolute quantification of metabolites, but this technique was not available to us in the present study. Nevertheless, in this study, in which we investigated NAA/creatine ratio in the white matter at a distance from the ICH, we have found a significant correlation between this ratio and stroke outcome, suggesting a new clinical application for proton MRS.

Decreases in NAA follow injury and degeneration of neurons in the lesion itself or surrounding tissue. NAA abnormalities, however, do not result solely from irreversible neuronal loss but also can be reversible, perhaps reflecting sublethal neuronal damage or deterioration of neural activity due to functional or metabolic stress. The decrease of NAA is demonstrated in regions with reduced cerebral blood flow but not completed ischemia. Normalization of the reduced NAA/creatine values has been observed after treatment for temporal lobe epilepsy or brain injury, indicating that NAA/creatine ratio may be a dynamic functional marker of neuronal activity. Our serial observation also disclosed a reversible reduction of NAA/creatine, in addition to continuous decrease. These changes could be interpreted to reflect reversible dysfunction or neuronal injury in the motor area distant from an ICH lesion, even after the size of the hematoma would have decreased (Figure 6).

The main result in our study, the correlation between Barthel Index score and NAA/creatine ratio in the primary motor area (Figure 5), is predictable because clinical outcome must be closely related to motor function, which also correlates with NAA/creatine ratio (Figures 4 and 5). However, it is noteworthy that a strongly significant correlation with

![Figure 4. Correlation between motor impairment of the extremities and NAA/creatine (Cr) ratio of white matter in primary motor area on affected side. Each circle represents a patient. Sums of arm and leg impairment scores of the NIH Stroke Scale were applied.](http://stroke.ahajournals.org/)

![Figure 5. Correlation between Barthel Index scores 2 months after onset and NAA/creatine (Cr) ratio of white matter in primary motor area on affected side at each period after onset. Each circle represents a patient.](http://stroke.ahajournals.org/)
Previous studies on animals have suggested the ischemic penumbra as an origin of the secondary progressing neuronal injury, which still remains controversial. In contrast, Qureshi et al reported in an animal study that there was no evidence of the ischemic penumbra in the first 5 hours after hemorrhage. In the acute period, systemic hypoxia caused by deteriorated cardiopulmonary function might also affect cerebral metabolites. Nevertheless, it is unlikely in our study because we excluded such severely affected patients who required ventilation and were unsuitable for MRS study in the acute stage, and the correlation between NAA/creatine and hematoma volume was observed only in the primary motor area of the affected side. This significant negative correlation indicates that a larger hematoma should result in deterioration of NAA/creatine in the acute stage, proposing mechanical compression and secondary induced surrounding ischemia as possible mechanisms of neural injury after deep-seated ICH.

It is also noteworthy that at 1 month there was no significant correlation detected between hematoma volume and NAA/creatine (Figure 3), which may remain constant or increase in some patients with large hematoma. This observation may have been promoted by surgery, which can release continuous compression of the hematoma. These data also demonstrate that even a small amount of deep ICH can lead to remarkable reduction of NAA/creatine in chronic periods and that factors other than mechanical compression of the hematoma may affect NAA.

Reductions of NAA in the white matter of the primary motor area would at least indicate some delayed damage or functional disorder of neural fibers involving motor control, such as the corticospinal tract. A significant correlation was demonstrated between motor impairment and NAA/creatine in the motor area 2 weeks and 1 month later, whereas such correlation was not detected in acute periods (Figure 4). Pendlebury et al showed that the reduction of NAA at the level of the internal capsule after cortical infarcts correlated with motor deficits, indicating secondary injury of the corticospinal tract. In our results, NAA/creatine reduction in the motor area could suggest retrograde degeneration or injury of the corticospinal tract after axonal injury at the level of the internal capsule or corona radiata.

In addition to changes in the primary motor area, our patients with poor recovery have demonstrated severe reduction of NAA/creatine ratio extended over the bilateral frontal lobes (Figure 7). This observation should reflect neural damage of not only the corticospinal tract but also other
neural circuits around the basal ganglia, thalamocortical projection, association areas, and commissure fibers. The importance of these neural networks may also be emphasized by preservation of the NAA/creatinine ratio in patients with good and moderate outcomes (Figures 6 and 7). Previous studies have demonstrated that deep ICH can lead to a significant reduction of cerebral blood flow in the bilateral frontal lobes in patients with poor outcome. Abnormal NAA/creatinine ratios at 1 month should reflect the reduction of cerebral blood flow and following or coexisting deterioration of metabolism involving essential subcortical neuronal structure. Our findings, supported by other studies of poststroke patients using different modalities, have emphasized the possible contribution of premotor cortices and ipsilateral frontal lobes for functional recovery after stroke, from the point of view of cerebral metabolism. Longitudinal MRS examinations have demonstrated that the delayed gradual reduction of metabolites in frontal lobes correlates motor deficits with clinical outcome after deep ICH. Further investigation will be required, but our study suggests that proton MRS may provide beneficial information in assessing treatment for hemorrhagic stroke. The defect of NAA in the white matter suggests damage of the subcortical neural circuits, which is indicative of the importance of the network around the basal ganglia, thalamocortical projection, association areas, and commissure fibers as well as the descending projection of the corticospinal tract for poststroke recovery.

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References

In the preceding article, Kobayashi and colleagues have applied proton magnetic resonance spectroscopic imaging ($^1$H-MRSI) to study patients with intracerebral hemorrhage (ICH), an understudied illness that has been stubbornly resistant to treatment. They obtained spectra at 48 hours, 2 weeks, and 1 month after the acute event, and correlated the ratios of N-acetylaspartate (NAA) to creatine (Cr) with scores on the NIH Stroke Scale and the Barthel Index. They found that the NAA/Cr ratios correlated significantly with both measures at 2 and 4 weeks. Their results suggest that measurements of brain metabolites by $^1$H-MRSI may be useful in predicting outcome after an ICH.

Using $^1$H-MRSI, which yields an array of spectra, the authors studied a single axial slice encompassing the motor and premotor subcortical areas in the frontal white matter. Pathways that pass through the basal ganglia innervate these regions. Tissue regions were selected to avoid the hemorrhage and to exclude the cerebrospinal fluid. Frontal lobes were chosen for study because of their involvement in the motor functions of the brain and the relationship of those regions to the clinical measurements. Blood interferes with the measurement of NMR signals because of its paramagnetic properties. One potential problem with interpretation of the data is the reliability of the exclusion of blood from the voxels of interest. Although blood-containing voxels were identified visually and omitted from analysis, the course acquisition matrix ($16 \times 16$) results in blurring of spectral data from neighboring tissue. Another problem with the study was the small number of patients, and the inability to complete studies on all patients. Of the 20 patients, only 9 had studies at all 3 time points. Furthermore, patients with larger hemorrhage were more likely to undergo surgery, and the impact of the surgical procedures on the spectra is uncertain.

The authors found that at 48 hours and 2 weeks, NAA/Cr ratios correlated significantly with hematoma size; patients with larger hematomas had lower NAA/Cr. However, for reasons that are unclear, the measurements at 4 weeks failed to correlate with the size of the hematoma. This could have resulted from hematoma resolution without disruption of the surrounding tissues, which may have been displaced by the mass lesion. The NIH Stroke Scale correlated with NAA/Cr at 2 and 4 weeks, and it was possible to separate those with moderate and poor outcomes at 2 weeks; however, only those with a poor outcome maintained the low NAA/Cr at 4 weeks, which suggests that the larger masses would be more destructive.

An important finding of the study was that the unaffected side also showed a fall in the ratios of NAA/Cr in those with a poor outcome. The authors raise the possibility that the changes in NAA/Cr that are seen at a distance from the hematoma may be predictive of stroke outcome. They also saw a recovery of NAA/Cr ratios in the patients with moderate levels of injury. It is interesting to speculate on mechanisms to explain the observations. The authors note that reductions in frontal blood flow are recorded after ICH, and indeed this might explain reversible decreases in NAA/Cr. However, 2 recent studies, one in animals and the other in humans, have failed to show ischemia in the regions around an ICH. An alternative explanation emerging from experimental studies of ICH is that inflammation occurs around the mass lesion. The presence of inflammation could explain the fall in NAA/Cr through an increase in the glial mass and a rise in creatine in the absence of NAA changes, particularly in the group of patients with the moderate outcomes who had low levels of NAA/Cr at 2 weeks and a rise in the NAA/Cr at 4 weeks. Such a change was absent in those with the worst outcome, possibly due to the greater extent of tissue damage around those lesions. Finally, after traumatic brain injury, recovery of NAA remote from the site of primary injury was seen in patients whose cognitive status improved, which suggests recovery from remote metabolic depression. Because the frontal regions examined are linked by pathways to the basal ganglia sites of ICH, the results might be explained by the mechanism of diaschisis. Because of the limited understanding of the reversible changes that are seen in the NAA signals under a variety of neurological conditions, further studies will be needed to clarify this issue.

Advances have occurred in MRI, such as diffusion-weighted imaging, and in spectroscopy that have aided studies of the metabolic changes in ischemia. One recent
study\(^8\) used diffusion-weighted imaging for the location of voxels in the lesions. Need for localization may be further reduced by the introduction of spectroscopic imaging, which provides spectra from large areas of brain. The new, higher field magnets provide stronger signals with potentially improved spatial resolution and shorter data collection times. Moreover, the increasing availability of absolute concentrations rather than ratios of metabolites might lead to elucidation of mechanisms. Verification of spectroscopic data will also be needed, but because of the high mortality rate in ICH, studies correlating the \(^1\)H-MRSI data with autopsy data to confirm the histological basis may be possible. The authors of this study had a 50% success rate of studying these very ill patients in the first 48 hours. Improvements in ventilation methods, faster scanners, and improved access to the instruments for acute patients should improve on these numbers.

This is a timely study, given the renewed interest in hemorrhage, spurred by the increased risk of bleeding after thrombolysis.\(^9\) Despite the small number of patients and the lack of randomization because of the large number who had surgery, the results are encouraging that \(^1\)H-MRSI may be useful in ICH. Because of the limitations mentioned, this should be considered preliminary data that could form the basis for a larger, multicenter study to define a group of patients who are metabolically at risk and could benefit from treatment.

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References
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