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

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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.

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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. 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. It has been reported that clinical outcomes after deep ICH correlate with reduction of cerebral blood flow in bilateral frontal lobes. Cerebral ischemia is postulated to be one of the mechanisms of neural injury in the early periods after experimental ICH, but this is still controversial.

As for functional recovery after stroke, previous studies have indicated some possible role of premotor and somatosensory motor areas and unaffected frontal lobes, but the role of these areas is subject to controversy. Among hemorrhagic stroke, deep-seated ICHs are encountered most commonly and affect the striatocapsular area, which would lead to motor impairment. Karibe et al 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. 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. 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
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 primary motor and premotor 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. CSI has the advantage that spectra from a large amount of the brain parenchyma from the MR image can be chosen and collected in 1 acquisition. For the CSI studies, a 160-mm field of view was used. The volume of interest was localized with the use of PRESS with a 0.8-mm/m in-plane gradients and a 3-mm slice selection gradient to give a thickness of 20 mm. Phase encoding was applied in the sagittal and coronal directions before acquisition of the spin echo (repetition time, 1500 ms; echo time, 135 ms; acquisition time, 7 minutes). Data were acquired with water suppression to enable a first-order phase correction for the effects of eddy currents and field inhomogeneities. Estimation of choline (at a chemical shift of 3.2 ppm), creatine (at 3.0 ppm), and NAA (at 2.0 ppm) peak areas was made with the use of area integration with NUMARIS (Siemens) software, by 1 of 3 experienced operators who were blind to clinical data of the patients.

In this study we selected voxels located in the white matter of the primary motor and premotor areas on both sides to measure NAA and creatine. To select the voxels, the central sulcus was identified first with reference to MR images. Three voxels were picked from the premotor motor area, within the precentral gyrus, and 3 or 4 from the premotor area, ie, the posterior part of superior and middle frontal gyrus just anterior to the precentral gyrus. When a voxel contained cerebrospinal fluid or hematoma, it was excluded from further analysis. Therefore, 2, 3, or 4 voxels were selected from each area at every study. When the data could not demonstrate reliable MR spectra because of motion artifact, all the data from that session were discarded. The mean NAA/creatine ratio was calculated in each of the bilateral primary motor and premotor areas. We used the NAA/creatine ratio for evaluation because it could be measured easily and quickly, and creatine should have stable and constant signal intensity in the brain parenchyma. The correlation was examined between these NAA/creatine ratios and 3 other factors: hematoma volumes at onset, motor impairment at each time point, and clinical outcome 2 months after onset.

The intention of this study was to perform MRS serially at 3 time points: within 48 hours, at 1 week, and at 1 month after onset. However, some of patients could not complete this protocol in the acute stages because they were transferred to our institute too late for MR study within 48 hours after onset. Some patients were unsuitable for the studies in the acute stages because they could not enter the MR scanner safely without a respirator or they were unable to keep their head still without causing motion artifact because of severely disturbed consciousness. The first MRS was done within 48 hours, the second at a median of 2 weeks (range, 12 to 15 days), and the third at a median of 1 month (range, 28 to 35 days). All 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.

### 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 tumoral 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 an 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. Observers confirmed symmetrical placement of the voxels on the frontal lobes of both sides. CSI has the advantage that spectra from a large amount of the brain parenchyma from the MR image can be chosen and collected in 1 acquisition. For the CSI studies, a 160-mm field of view was used. The volume of interest was localized with the use of PRESS with a 0.8-mm/m in-plane gradients and a 3-mm slice selection gradient to give a thickness of 20 mm. Phase encoding was applied in the sagittal and coronal directions before acquisition of the spin echo (repetition time, 1500 ms; echo time, 135 ms; acquisition time, 7 minutes). Data were acquired with water suppression to enable a first-order phase correction for the effects of eddy currents and field inhomogeneities. Estimation of choline (at a chemical shift of 3.2 ppm), creatine (at 3.0 ppm), and NAA (at 2.0 ppm) peak areas was made with the use of area integration with NUMARIS (Siemens) software, by 1 of 3 experienced operators who were blind to clinical data of the patients.

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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 (F,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
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/creatine decreased severely in some patients with even small-volume hematoma at 1 month. No correlation was detected between hematoma volume and NAA/creatine 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/creatine in the primary motor area on the affected side. Within 48 hours, there was no correlation between NIH Stroke Scale score and NAA/creatine ratio. There were significant correlations between them 2 weeks and 1 month after stroke ($r = -0.75$, $P < 0.01$ and $r = -0.806$, $P < 0.001$, respectively).

Figure 5 indicates the correlation between NAA/creatine 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/creatine 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/creatine 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 ($F_{3,6} = 8.73$, $P < 0.05$). 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/creatine 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/creatine ratio of the moderate outcome subgroup increased to be significantly larger than that of the poor outcome subgroup, in which NAA/creatine decreased further.

Motor Impairment, Clinical Outcome, and NAA/Creatine Ratios in Premotor Area and Primary Motor Area on Unaffected Side

NAA/creatine 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...
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/creatinine 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/creatinine 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/creatinine (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/creatinine 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/creatinine 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/creatinine 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/creatinine ratio extended over the bilateral frontal lobes (Figure 7). This observation should reflect neural damage of not only the corticospinal tract but also other

**Figure 6.** Serial changes of NAA/creatine (Cr) ratio in primary motor area on affected side. Data were divided into 3 categories according to the Barthel Index score at 2 months: good recovery (75 points), moderate recovery (45 to 70 points), and poor recovery (≤40 points). ANOVA demonstrates significant differences among the data at each time point (P<0.001) and among the subgroups partitioned by Barthel Index scores (P<0.05) and a significant interaction between time course and subgroups (P<0.005). At 2 weeks and 1 month there were significant differences among the data of these groups. Vertical bars indicate SEs. *P<0.05.

The long-term clinical outcome was detected as early as 2 weeks after onset and that sequential changes of the NAA/creatinine ratio follow various curves depending on their clinical outcomes. The increase of ratios in patients with moderate outcome was impressive (Figure 6), indicating that improvement of neural activity could lead to better functional recovery. The period between 2 weeks and 1 month after onset corresponds with the term when functional recovery should be accelerated after stroke. Our present study, concerning metabolites and their sequential changes, requires further investigation but highlights the possibility that proton MRS may provide clinically beneficial information and may help to predict clinical outcome after deep ICH.

Our study showed a significant correlation between hematoma volume and NAA/creatinine ratio in the primary motor area within 48 hours and at 2 weeks after stroke. Such a decrease may be small within 48 hours because paired t test did not detect a significant difference between both sides (Figure 3). In 4 patients with a small hematoma (<12 mL), the ratios were almost equal on both sides or larger on the affected side than the unaffected side within 48 hours. These results, however, indicate that neural damage or dysfunction in the primary motor area could occur in the acute stage.

**Figure 7.** Correlation between Barthel Index scores 2 months after onset and NAA/creatinine (Cr) ratio of white matter in premotor area on affected side (A) and premotor (B) and primary motor (C) areas on unaffected side measured 1 month after onset.
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/creatine 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/creatine 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 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 (1H-MRSI) to study patients with intracerebral hemorrhage (ICH), an understudied illness that has been stubbornly resistant to treatment.1 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 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 animals2 and the other in humans,3 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.4 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.6 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.7 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 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 ¹H-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. Despite the small number of patients and the lack of randomization because of the large number who had surgery, the results are encouraging that ¹H-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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