Temporal Lobe Epilepsy: Bilateral Hippocampal Metabolite Changes Revealed at Proton MR Spectroscopic Imaging

PURPOSE: To determine which proton magnetic resonance (MR) spectroscopic imaging measures are best for lateralizing the seizure focus in patients who have temporal lobe epilepsy with and in those without hippocampal atrophy on MR images, the extent of contralateral abnormalities, and whether there is a correlation between MR spectroscopic imaging findings and surgical outcome.

MATERIALS AND METHODS: MR spectroscopic imaging was performed in 16 adult patients with temporal lobe epilepsy and unilateral electroencephalographic findings and in 16 adult control subjects. Eleven patients underwent surgery; all patients underwent MR imaging. RESULTS: Nine patients had hippocampal atrophy on MR images. An ipsilateral decrease in the N-acetylaspartate concentration or the ratio of N-acetylaspartate to the sum of creatine and choline (N-acetylaspartate/[creatine + choline]) was found in all patients. Decreased contralateral N-acetylaspartate concentration, N-acetylaspartate/[creatine + choline], or N-acetylaspartate concentration and N-acetylaspartate/[creatine + choline] were detected in eight patients (50%), which suggests bilateral abnormalities not detected with MR imaging. In the five patients who underwent surgery and did not show hippocampal atrophy on MR images, successful and unsuccessful outcomes were correctly predicted with N-acetylaspartate concentration.

CONCLUSION: Decreased N-acetylaspartate concentration is not due solely to hippocampal atrophy. Contralateral abnormalities are much more frequent than expected. MR spectroscopic imaging is valuable in the presurgical evaluation of epilepsy.

Electroencephalography (EEG) is the standard of reference for lateralizing the seizure focus in patients with intractable temporal lobe epilepsy. Patients with nonlesional temporal lobe epilepsy diagnosed with a unilateral focus at EEG and with hippocampal atrophy ipsilateral to the seizure focus at magnetic resonance (MR) imaging have an 86%-97% chance of being free of seizures after temporal lobectomy (1-3). However, in the absence of hippocampal atrophy on MR images, the prognosis for a seizure-free outcome is only about 50%.

Recently, this laboratory (4,5) and others (6-13) showed that proton MR spectroscopy (6,8,10,11) and MR spectroscopic imaging (4,5,7,9,12,13) can be used to lateralize the seizure focus in temporal and frontal lobe epilepsy. However, different MR spectroscopic measures were used in the different studies, and, in some cases, contradictory results were obtained. Several authors found ipsilateral decreases in the N-acetylaspartate signal intensity (4,7,8), the N-acetylaspartate-creatine ratio (5,6,9,13), the N-acetylaspartate-choline ratio (12), or the N-acetylaspartate-creatine-choline ratio (N-acetylaspartate/[creatine + choline]) (10,11). Although the hippocampus is the most important region in temporal lobe epilepsy, only Hugg and colleagues (4) and Hetherington and co-workers (13) evaluated spectra predominantly from the hippocampus.

The purposes of this study were, therefore, not only to confirm and extend previous findings, but also to determine which MR spectroscopic imaging measures allow optimal lateralization of the seizure focus and which allow the best prediction of surgical outcome. The specific goals of this study were to determine the pattern of metabolite changes that provides the greatest concordance with EEG findings, to determine whether reduced N-acetylaspartate is due to hippocampal atrophy, to determine the extent to which contralateral abnormalities occur in patients with EEG-defined unilateral temporal lobe epilepsy, and to determine which metabolite measures best correlate with successful surgical outcome.

MATERIALS AND METHODS

Patients and Control Subjects

Sixteen patients (nine men, seven women; aged 21-49 years; mean age ± standard deviation, 35.9 years ± 8.9) with a unilateral temporal lobe seizure focus at EEG were examined. All patients were examined...
examined at the Northern California Comprehensive Epilepsy Center (San Francisco, Calif); none of the patients had clinical or EEG evidence suggestive of a second seizure focus. The seizure focus was localized by means of scalp (including sphenoidal) and, as necessary, subdural electrode recordings. Only patients whose ictal recordings demonstrated either localized voltage attenuation or rhythmic sharp activity that preceded the onset of the clinical seizure were included.

Eleven of the 16 patients underwent surgery. They were followed up for 8-20 months, and their seizure outcome was defined by using the Engel classification (14). MR spectroscopic imaging data also were obtained in 16 healthy subjects (11 men, five women; aged 23-56 years; mean age, 33.3 years ± 7.9). Informed consent was obtained from all patients and control subjects before the examination.

Diagnostic MR Imaging

All patients separately underwent MR imaging. MR imaging examinations were performed with a 1.5-T system (GE Medical Systems, Milwaukee, Wis), and the following image data sets were acquired: an initial sagittal T1-weighted spin-echo data set (with a repetition time [TR] of 600 msec and a minimal echo time [TE]) through the hippocampus and temporal lobes; an axial T2-weighted spin-echo data set (with a TR of greater than 2,000 msec and TEs of 35 and 80 msec [>2,000/35,80]); a three-dimensional spoiled gradient-echo data set (with a TR of 50 msec and a minimal TE, a 40° flip angle, and a 1.5-mm section thickness); a coronal T2*-weighted gradient-echo data set (with 500/15-34 and a 20° flip angle); and a coronal T2-weighted fast spin-echo data set (with a 512 × 512 matrix).

MR images were read by a neuroradiologist blinded to the seizure lateralization findings. Nine patients had unilateral hippocampal atrophy; four also had a unilateral focus of increased T2 signal intensity within the hippocampus. No abnormalities were found on the MR images obtained in the other seven patients. This high percentage of patients without hippocampal atrophy does not reflect the statistical distribution of atrophy in patients with intractable temporal lobe epilepsy in the general population.

MR Spectroscopic Imaging

In all cases, the proton MR spectroscopic imaging studies were acquired and analyzed without knowledge of the side of the seizure focus. The spectra were acquired with a 1.5-T Magnetom Vision unit (Siemens, Erlangen, Germany) by using a standard, circularly polarized head coil. To reduce motion of the head, a vacuum-molded head holder (Vac-Pac; Olympic Medical, Seattle, Wash) was used. For localization, two-dimensional fast low-angle shot (FLASH) images (200/6) were acquired in coronal, sagittal, and oblique transverse orientations.

The transverse images were parallel to the long axis of the hippocampus, with the center section positioned through the center of the hippocampus. A two-dimensional MR spectroscopic imaging sequence (1.8/135) with point-resolved spectroscopic PRESS volume selection (average size of 72.5 × 97.7 × 15.0 mm3) was used with the volume parallel to the transverse images and including both hippocampi. An MR spectroscopic imaging field of view of 210 × 210 mm was used with circular k-space sampling equivalent to a maximum of 24 × 24 phase-encoding steps (15). Another measurement parameter was 1,800/135, which resulted in a measurement time of 13 minutes. Figure 1a shows a sagittal FLASH localizer image with the PRESS MR spectroscopic imaging box superimposed. Corresponding oblique transverse FLASH localizer images with spectra from the left and right hippocampi that were obtained in a healthy control subject, in a patient with temporal lobe epilepsy and hippocampal atrophy, and in a patient with temporal lobe epilepsy and no hippocampal atrophy are shown in Figure 1b-1d.

Quantitation

The unsuppressed water signal intensity was used as an internal standard in a
second MR spectroscopic imaging examination with otherwise identical parameters (16,17), which guaranteed that the water and metabolite signal intensities were derived under identical conditions. The quantitation method required correction of metabolite and water signals for T1 and T2 relaxation times, additional correction of the water concentration (aqueous fraction), and correction of the metabolite signals for the number of protons in the metabolite molecules. Metabolite concentrations are reported in millimoles per liter.

Arbitrarily chosen mean metabolite relaxation times from the literature (five T1 and eight T2 values) (18–24) for N-acetylaspartate (T1 = 1.31 seconds ± 0.19 [standard deviation], T2 = 0.37 seconds ± 0.07), creatine (T1 = 1.29 seconds ± 0.14, T2 = 0.20 second ± 0.03), choline (T1 = 1.31 seconds ± 0.11, T2 = 0.33 second ± 0.07), and water (T1 = 0.95 second and T2 = 0.10 second [25]) in gray matter were used. It was assumed that metabolite relaxation times were not substantially different between gray and white matter.

Metabolite concentrations in millimoles per liter were calculated as $C_{met} = \frac{cH_2O[S_{met} \times c_{T1(H_2O)} \times c_{T2(H_2O)}] \times z + S_{H_2O}}{c_{T1(H_2O)} \times c_{T2(H_2O)} \times n}$, where $C$ is the concentration, $met$ is metabolite, $S$ is the peak area of the indicated resonance, $c$ is a correction factor, and $n$ is the number of protons in the metabolite molecule resonance. Correction factors were calculated as follows: $c_{T1} = 1 - e^{-TR/T1}$, and $c_{T2} = e^{-TE/T2}$.

The water signals were also corrected for the receiver gain difference between the MR spectroscopic imaging experi-
ments performed with and those performed without water suppression. A hippocampal (gray matter) water content of 88% (i.e., 44.45 mol/L) was assumed for calculation of $C_{\text{Hill}}$ (26). For the detection of statistically significant variations in the water signal and their influence on metabolite concentrations, metabolite and water signals were also corrected for coil loading. This was done by normalizing the metabolite signal according to the transmitter reference voltage (27-29).

**MR Spectroscopic Imaging Processing**

Postprocessing of the MR spectroscopic imaging data was done with software provided by Siemens (LUISE). A k-space apodization that resulted in an effective voxel size of approximately 4 cm$^3$ and zero-filling to $32 \times 32$ k-space points was applied before the spatial Fourier transformation. Zero filling from 512 to 1,024 time-domain data points and Gaussian multiplication that corresponded to 0.6-Hz line broadening were performed before the time-domain Fourier transformation. Spectral phasing and a polynomial baseline correction were also performed.

Voxels that included primarily hippocampal gray matter were selected, and the signals of N-acetylaspartate, creatine, and choline were curve fit with LUISE with the assumption of Gaussian line shapes. The profile of the 180° selective pulse in this direction was suboptimal in the first two voxels from the anterior and posterior borders of the volume of interest. This and the chemical shift displacement error of 2.4 ppm between N-acetylaspartate and choline in the in-plane directions (0.8-mT/m gradient strength) lead to disturbed metabolite-metabolite and metabolite-water ratios in these voxels. Therefore, these voxels were avoided. An average of five voxels (range, two to seven voxels) were selected in each hippocampal region. Mean values of spectra from those voxels are reported, and added spectra are shown in Figure 1c and 1d.

**MR Spectroscopic Imaging Lateralization**

Lateralization by using MR spectroscopic imaging measures was performed in two different ways with the N-acetylaspartate/(creatine + choline) ratio and the N-acetylaspartate concentration as determined with the absolute quantitation technique (16). The first lateralization involved comparison of metabolite concentrations and metabolite peak ratios in the ipsilateral hippocampal region with those on the opposite side. This comparison is based on intradinidividual asymmetry, and no statement about an absolute decrease in metabolite concentration or metabolite peak ratio can be made. In the blinded evaluation, the side with the lower value was called the affected side.

The second lateralization involved comparison of patient hippocampal data with healthy control subject hippocampal data. Values more than 2 standard deviations below the mean of the control subject data were considered to be abnormal. Thus, there were three possibilities for lateralization findings: unilateral, bilateral, or normal.

**Statistical Analysis**

Statistical analyses of the MR spectroscopic imaging data were performed by using analysis of covariance and repeated measures analysis of variance. The N-acetylaspartate/(creatine + choline) ratio and N-acetylaspartate concentration were analyzed with Bonferroni corrections for multiple comparisons and the Duncan multiple range test (30). N-acetylaspartate-creatine and N-acetylaspartate-choline ratios and the concentrations of choline and creatine are presented in secondary analyses for descriptive purpose only and without statistical comparisons.

**RESULTS**

**Metabolite Measures That Allow Optimal Lateralization**

The concentrations of N-acetylaspartate, creatine, and choline, as well as the N-acetylaspartate/(creatine + choline), N-acetylaspartate-creatine, and N-acetylaspartate-choline metabolite peak ratios, were evaluated. In the patients, the N-acetylaspartate ratios and N-acetylaspartate concentration were substantially decreased in the ipsilateral hippocampus, which confirmed previous study findings. In addition, N-acetylaspartate measures were decreased in the contralateral hippocampus in patients with temporal lobe epilepsy as compared with the measures in control subjects.

To determine the best lateralization criteria, we looked for (a) which measures were in best agreement with EEG results by comparing the sides with the lower MR spectroscopic imaging measures with the EEG lateralization findings and (b) which measures had the largest difference between the mean values in the patients compared with those in the control subjects. N-acetylaspartate/(creatine + choline) provided concordance with EEG lateralization findings in a left-versus-right hemisphere comparison in all patients. The largest difference in means was in the N-acetylaspartate concentration. The N-acetylaspartate concentration did not allow correct lateralization in three patients without atrophy in a left-versus-right comparison but indicated greater bilateral abnormalities (i.e., abnormalities in both the ipsilateral and contralateral hippocampi) in a comparison with control subject data. In 15 of 16 patients, ipsilateral N-acetylaspartate concentration and N-acetylaspartate/(creatine + choline) were below the mean control values.

N-acetylaspartate/(creatine + choline) and N-acetylaspartate concentration in an ipsilateral versus contralateral comparison in patients and in a left-versus-right comparison in control subjects are plotted in Figure 2. Table 1 lists the mean values for all MR spectroscopic imaging measures in the control group and for the same and opposite sides in patients with and in patients without hippocampal atrophy.

Statistical analysis was performed for N-acetylaspartate concentration and N-acetylaspartate/(creatine + choline). No statistically significant left-versus-right differences in the control group were found. Within the control and patient groups, no
Table 1
Metabolite Concentrations and Metabolite Peak Ratios in Patients and Control Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Metabolite Concentration</th>
<th>Metabolite Peak Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NAA</td>
<td>Choline</td>
</tr>
<tr>
<td>Control subjects (n = 16)</td>
<td>11.6 ± 1.3</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>All patients (n = 16)</td>
<td>8.1 ± 1.5 (−30.2)*</td>
<td>2.6 ± 0.4 (0)</td>
</tr>
<tr>
<td>Patients with hippocampal atrophy (n = 9)</td>
<td>9.4 ± 1.3 (−19.0)*</td>
<td>2.4 ± 0.5 (−11.1)</td>
</tr>
<tr>
<td>Ipsilateral hemisphere</td>
<td>7.6 ± 1.5 (−34.5)*</td>
<td>2.5 ± 0.4 (−3.8)</td>
</tr>
<tr>
<td>Contralateral hemisphere</td>
<td>9.7 ± 1.2 (−16.3)*</td>
<td>2.5 ± 0.5 (−3.8)</td>
</tr>
<tr>
<td>Patients without hippocampal atrophy (n = 7)</td>
<td>8.6 ± 1.4 (−25.9)*</td>
<td>2.7 ± 0.4 (+3.8)</td>
</tr>
<tr>
<td>Ipsilateral hemisphere</td>
<td>8.9 ± 1.2 (−23.5)*</td>
<td>2.4 ± 0.6 (−11.1)</td>
</tr>
<tr>
<td>Contralateral hemisphere</td>
<td>8.2 ± 1.1 (−16.5)*</td>
<td>2.4 ± 0.6 (−11.1)</td>
</tr>
</tbody>
</table>

Note.—Data are mean ± standard deviation. Numbers in parentheses are percentage change. NAA = N-acetylaspartate.
* Significantly different from the control mean (P < .05) with Duncan multiple range test.

Relationship of MR Spectroscopic Imaging Data to Surgical Outcome

The final aim of the study was to investigate the correlation between MR spectroscopic imaging findings and seizure surgery outcome. Six patients with hippocampal atrophy underwent surgery; five became seizure free (five patients, class I; one patient, class III). Both N-acetylaspartate concentration and N-acetylaspartate/(choline + creatine) in these six patients provided lateralization findings concordant with EEG findings.

Five patients without hippocampal atrophy underwent surgery. In two of them, N-acetylaspartate concentration and N-acetylaspartate/(choline + creatine) findings were concordant with EEG findings and the patients became seizure free (class I). In the three remaining patients, the N-acetylaspartate/(choline + creatine) ratio resulted in lateralization findings discordant with those of the EEG left-versus-right comparison; however, the N-acetylaspartate concentration was equally low on both sides or was even lower on the opposite side, and in two patients it was ipsilateral within the control mean ± 2 standard deviation range. These three patients continued to have seizures after surgery, although the seizure frequency decreased.
Two of the seven seizure-free patients also showed contralateral abnormaly low N-acetylaspartate concentrations, but these decreases were less than the ipsilateral decrease. The individual asymmetries between ipsi- and contralateral N-acetylaspartate concentrations in the patients who were followed up after surgery are shown in Figure 3.

In summary, in seven patients with unilateral temporal lobe epilepsy who underwent surgery, a concordant decrease in N-acetylaspartate concentration, in N-acetylaspartate/(creatine + choline), or in both in the ipsilateral hippocampus was predictive of surgical success. Five of these seven patients had ipsilateral atrophy. In three patients without ipsilateral atrophy, a bilateral equally decreased or contralateral lower N-acetylaspartate concentration was associated with poor surgical outcome.

**DISCUSSION**

The results confirm previous study findings that proton MR spectroscopic imaging measures allow lateralization of the seizure focus in temporal lobe epilepsy. Statistically significant decreases in N-acetylaspartate concentration and N-acetylaspartate/(creatine + choline) as compared with control data were found in the ipsilateral hippocampus in patients with and in patients without hippocampal atrophy. N-acetylaspartate/(creatine + choline) was found to be the most sensitive measure for lateralization in concordance with EEG results. Contralateral low N-acetylaspartate concentration or N-acetylaspartate/(creatine + choline) was detected in 50% of the patients. Furthermore, in this study, MR spectroscopic imaging findings of decreased contralateral N-acetylaspartate concentration were related to surgical outcome.

**Metabolite Measures That Allow Optimal Lateralization**

N-acetylaspartate/(creatine + choline) was in complete concordance with EEG lateralization in left-versus-right comparisons (Fig 2a). The N-acetylaspartate-choline ratio was not concordant in one case, and the N-acetylaspartate-creatine ratio and N-acetylaspartate concentration (Fig 2b) were discordant in three cases. The differences in concordance between these measures are suggestive of a greater reliability of the sum of creatine and choline than either one alone, although not to a level of statistical significance. A possible reason is that the creatine and choline signals often partially overlap; this results in inaccuracies in the individual line fits for these metabolites, even though the sum of the fits for these two metabolites remains accurate.

All previous proton MR spectroscopic studies of temporal lobe epilepsy found decreased ipsilateral N-acetylaspartate as an absolute decrease in the N-acetylaspartate signal (4,7), as a decrease in the N-acetylaspartate concentration (8), or as a decrease in the N-acetylaspartate-creatine (5,6,9,13), in the N-acetylaspartate-choline ratio, or in both (10–12). Unfortunately, no unique measure was entirely successful in lateralization in these previous studies. For example, Breiter and colleagues (8) found an ipsilateral decreased N-acetylaspartate concentration in all their patients but no statistically significant decrease in the N-acetylaspartate-creatine ratio. Cendes and co-workers (9) preferred to use the N-acetylaspartate-creatine ratio as the criterion for lateralization, whereas Ng and colleagues (12) found the N-acetylaspartate-choline ratio to be the most sensitive measure. Only a few studies have reported changes in creatine and choline, and these studies have had contradictory results. Layer and colleagues (7) reported ipsilaterally decreased creatine in temporal lobe epilepsy, whereas Connelly and colleagues (10) and Gadian and colleagues (11) found a 15% increase. By using the method of Connelly et al (10) and Gadian et al (11) (that is, by correcting the metabolite signal for coil loading), we did not find a change in the creatine signal in the seizure focus. However, our calculations of the creatine concentration on the basis of the water signal did show a trend for a decreased concen-

| Table 2 |

<table>
<thead>
<tr>
<th>Patient Characteristics and Lateralization of Seizure Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No./Age (y)/Sex</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Patients with hippocampal atrophy</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

| Patients without hippocampal atrophy | 2/49/F | MTS | L | L | L | N/A |
|                                      | 4/43/M | MTS | L | L | L | N/A |
|                                      | 5/26/M | N | L | L | L | N/A |
|                                      | 9/36/M | N/A | L | L | L | N/A |
|                                      | 11/41/F | N/A | L | L | L | N/A |
|                                      | 12/28/M | MTS | R | R | R | N/A |
|                                      | 13/44/M | MTS | R | R | R | N/A |

| Note. | B = bilateral, B:L = bilateral with dominant left hemispheric lesions, B:R = bilateral with dominant right hemispheric lesions, L = left, MTS = mesial temporal sclerosis, N = normal, N/A = not applicable, NAA = N-acetylaspartate, R = right. |

* Determination of hemisphere on the basis of patient data at least 2 standard deviations below the control subject data.
The decrease in N-acetylaspartate 

was reduced ipsilaterally in patients 

with temporal lobe epilepsy, which is 

in agreement with our findings.

The major advantage of quantitaiting 

MR spectroscopic imaging data by 

using the in vivo water signal is that 

water signals are obtained under exactly 

the same conditions as the metabolite 

signals. The signals are obtained from 

the same anatomical region; therefore, 

the method is insensitive to variations 

in $B_0$ and $B_1$. There is no need to 

rescan or recalibrate flip angles, and long-term 
time-dependent instrument instabilities 

are inherently accounted for. Another 

advantage of this method is that it is 

possible to determine the extent to 

which the decrease in the N-acetylaspar-

tate signal is due to an increase in the 

amount of water in the voxel. The 

absence of a statistically significant 

negative correlation between the 

water signal and the N-acetylaspartate 

signal rules out statistically signifi- 

cantly varying partial volumes of 

perihippocampal CSF in the analyzed 

MR spectroscopic imaging voxels, be- 

cause CSF contains no MR-detectable 

N-acetylaspartate concentration (33,34). 

Nevertheless, there are several po-

tential error sources in the use of ab-

solute units. The disadvantage that 

corrections for metabolite relaxation 

times $T_1$ and $T_2$ are necessary is in-

herent in MR spectroscopic imaging 

quantitation methods, because time 

limitations for in vivo studies do not 

allow collection of fully relaxed spec-

tra. In addition to the uncertainties in 

the evaluation of $T_1$ and $T_2$ (no hip-

pocampal metabolite relaxation times 

have been reported so far), a bi- or 

multieponential $T_2$ decay for water 

is caused by different types of brain 

material (CSF, gray or white matter, 

blood vessels), especially in CSF be-

cause of the long $T_2$ (35). Further-

more, pathologic conditions can alter 

metabolite relaxation rates.

In contrast with single-voxel MR 

spectroscopic studies, the determina-

tion of the metabolite $T_1$ and $T_2$ in 

the individual MR spectroscopic im-

aging voxel is much too time-consum-

ing to be applicable in a patient exami-

nation. Shorter $T_E$s would reduce the 

error introduced by the estimated $T_2$ 

values. The reasons for using a $T_E$ of 

135 msec for both MR spectroscopic 

imaging measurements were that we 

wanted to use identical sequence and 

instrumentation parameters and that 

the metabolite resonance evaluation 

of short-$T_E$ spectra is more difficult 

because of interfering resonances 

from macromolecules and substan-

tially worse water and lipid suppres-

sion.

An MR spectroscopic imaging-

specific disadvantage of the absolute 

quantitation method presented here 

is that Gibb ringing effects may lead 

to over- or underestimation of the 

water content in a specific voxel. How-

ever, Gibb ringing can be minimized 

by means of data processing with 

nonuniform k-space weighting func-

tions (36) (although some spatial reso-

lution is sacrificed with this approach), 

by means of a further increase in the 

number of phase-encoding steps, or 

by means of a combination of both 

methods. One particular disadvan-

tage of the water reference method 

is that measurement time is prolonged 

because of the need to collect the wa-

ter signal. The higher probability of 

patient movement with prolonged 

measurement time does indirectly 

affect the accuracy of the method.

The water content is usually not 

uniform over the whole volume of 

interest. The concentration varies 

with the composition of brain tissue, 

CSF, and, possibly, abnormalities. This 

affects any quantitation method. For 

the water reference method, this has 

the disadvantage that the concentra-

tion of the water standard is not pre-

cisely known. Because of all these 

limitations, a large error range is in-

trinsic in the quantitation of metabo-

lites in absolute units in MR spectro-

scopic and MR spectroscopic imaging 

studies.

In addition to these general ob-

staciles, the hippocampus is a small 

structure that mainly consists of gray 

matter surrounded by temporal lobe 

white matter and CSF in the temporal 

horn. It should be emphasized that 

even though this method reports 

quantitative data in millimoles per 
liter, the current method does not 

quantitate the heterogeneous tissue 

compartmentation of the voxel from 

which the signals arise. Nevertheless, 

our results demonstrate that any in-

trusion of CSF associated with hip-

pocampal atrophy is too small to be 

statistically significant in the quanti-

tation method presented here.

A possible improvement could be 

attained from an MR image segmen-

tation of the tissue in each volume of 

interest (37). In theory, the tissue 

composition of gray and white matter 

and CSF and the amount of tissue 

water used to quantitate the tissue 

N-acetylaspartate concentration could 

be determined. Also, the effective MR 

spectroscopic imaging voxel size could 

be reduced by extending the number of 

phase-encoding steps to $24 \times 24$ 

instead of $24 \times 24$ and by applying a 

less effective k-space filter.
Relationship of Decreased N-Acetylaspartate Concentration to Hippocampal Atrophy

The finding that N-acetylaspartate was also reduced in ipsilateral nonatrophic hippocampi and without a simultaneous decrease in creatine and choline in all patients further indicates that the reduced N-acetylaspartate concentration is not due to atrophy alone. The decrease in the hippocampal N-acetylaspartate concentration can be explained neither in terms of atrophy alone nor in terms of the small increase in the hippocampal water signal.

These results suggest that MR spectroscopic imaging depicts neuron loss and that growth of glial cells (gliosis) has replaced lost neurons, which prevents atrophy. This is supported by histopathologic evidence of gliosis in temporal lobe epilepsy. The finding that MR spectroscopic imaging measures allowed lateralization in patients without atrophy or other abnormalities at MR imaging suggests that MR spectroscopic imaging is a more sensitive marker of hippocampal abnormality in temporal lobe epilepsy than qualitative MR imaging.

Bilateral Abnormalities

Articles on previous neuroimaging studies (eg, on positron emission tomography; MR imaging) have not reported much bilateral disease (38-41). The reduced N-acetylaspartate concentration, N-acetylaspartate/creatine + choline), or both in the contralateral hippocampus in 90% of patients with unilateral seizure foci suggests that bilateral hippocampal abnormalities are more common than previously thought. Contralateral abnormalities in proton spectra from the temporal lobe were also found by Connelly and colleagues (10) in 40% and by Ng and colleagues (12) in 18% of their patients with unilateral temporal lobe epilepsy. In a carefully performed autopsy study of temporal lobe epilepsy, Margerison and Cornells (42) found structural abnormalities of both hippocampi in 30% of their patients.

The importance and interpretation of the contralateral decreases in N-acetylaspartate are speculative at this time. These changes could be nonspecific and unrelated to epilepsy. However, contralateral metabolite changes are defined in comparison with data obtained in healthy control subjects age matched to the patients, and we cannot identify any factor other than epilepsy or its treatment that might have caused these changes. We determined that patients with neocortical epilepsy do not show decreased hippocampal N-acetylaspartate (43). Therefore, it seems that these hippocampal changes are not a nonspecific response to seizure activity or treatment but are associated with mesial temporal lobe epilepsy.

Furthermore, it is possible that the observed bilateral abnormalities are associated with (and possibly responsible for) poor surgical outcome.

Relationship of MR Spectroscopic Imaging Data to Surgical Outcome

MR spectroscopic imaging findings were predictive of poor outcome in three patients who underwent seizure surgery. Contralateral abnormalities were not always associated with poor surgical outcome, but the three patients who had either bilaterally equal N-acetylaspartate concentrations or a more marked reduction in N-acetylaspartate concentration on the opposite side as compared with the same side did not become seizure free after surgery. This emphasizes the value of absolute quantitation of MR spectroscopic imaging data. However, these results need to be confirmed in a larger cohort with longer postsurgical follow-up.

In conclusion, the results presented here show that decreased N-acetyl aspartate concentration is not due solely to hippocampal atrophy and that contralateral abnormalities are much more common than previously thought. More important, our findings emphasize the value of MR spectroscopic imaging in the presurgical evaluation of epilepsy.

Acknowledgment: We thank Diane Amend, PhD, for her help with the statistical analysis.

References

22. Danielsen E, Henriksen O. Absolute quantitative proton NMR spectroscopy based on the suppression of water and m. 7311-318.


