Value of Single-Voxel Proton MR Spectroscopy in Temporal Lobe Epilepsy

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PURPOSE: To study the value of different parameters derived from single-voxel proton MR spectroscopy of the mesial temporal lobes in the lateralization of the epileptogenic zone in patients with temporal lobe epilepsy. **METHODS:** We studied 12 healthy volunteers and 21 patients with temporal lobe epilepsy refractory to medical treatment, which was clearly lateralized with electroencephalography (EEG) and MR imaging. The mesial temporal lobes were investigated with single-voxel proton MR spectroscopy using a point-resolved spectroscopic sequence with an echo time of 135 milliseconds. The normalized concentration of *N*-acetylaspartate (NAA), creatine (Cr), and choline-containing compounds (Cho), and the metabolite ratios NAA/Cho+Cr, NAA/Cr, Cho/Cr, and NAA/Cho were calculated from the spectra. Using these values and an asymmetry index, we assigned the patients to one of five lateralization categories. **RESULTS:** The most consistent MR spectroscopic parameter for clear lateralization was the NAA/Cho+Cr ratio, followed by the NAA ratio. But with an adequate asymmetry index, the epilepsy in 17 (81%) of 21 patients could be lateralized by EEG and MR imaging with both parameters concordantly. Symmetric bilateral abnormalities were found in four of the 21 patients with NAA/Cho+Cr and in only one of the 21 patients with NAA. With both parameters, no contradictory lateralization was found; however, this was indeed the case with the remaining ratios, NAA/Cr, Cho/Cr, and NAA/Cho, in two, three, and one of the patients, respectively. A statistically significant decrease in NAA was found on the epileptic side, but also on the contralateral side. **CONCLUSION:** With an adequate asymmetry index, NAA/Cho+Cr and NAA are equally sensitive in predicting the side of involvement in patients with unilateral temporal lobe epilepsy.

Index terms: Magnetic resonance, spectroscopy; Seizures

AJNR Am J Neuroradiol 18:1131–1139, June 1997

Proton magnetic resonance (MR) spectroscopy can show abnormalities in the temporal lobes of patients with temporal lobe epilepsy (1–12)(A. Connelly, D. G. Gadian, G. D. Jackson, et al, "1H Spectroscopy in the Investigation of Intractable Temporal Lobe Epilepsy," in: *Proceedings of the Society of Magnetic Resonance in Medicine,* Berlin, Germany: 1992:234; and E. Achten, P. Boon, J. De Poorter, F. Vandamme, K. L. Verstraete, M. Kunnen, "Multiparameter MR Imaging and MRS of the Temporal Lobe in Normal Subjects and in Patients with Complex Partial Seizures," in: *Proceedings of the Society of Magnetic Resonance in Medicine,* New York, NY: 1993:482), and this technique can assist in the lateralization of the epileptogenic zone (3–7, 9–12)(Connelly et al, "1H Spectroscopy..."; Achten et al, "Multiparameter..."). Patients with medically uncontrolled partial seizures of temporal lobe origin are possible candidates for surgery, but first, the seizure focus must be correctly localized and lateralized by means of scalp electroencephalography (EEG) and video EEG monitoring, as well as by neuropsychological examination and structural (MR) and metabolic (positron emission tomography [PET] or single-photon emission computed tomography [SPECT]) imaging (13–16).

MR imaging can show structural abnormalities in 70% to 90% of patients with temporal lobe epilepsy (13, 14, 17). As many as 30% of these

Received September 25, 1996; accepted after revision December 30.

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AJNR 18:1131–1139, Jun 1997 0195-6108/97/1806–1131

patients have normal or nearly normal findings on routine MR imaging studies of the brain, and subtle abnormalities can only be found with state-of-the art MR imaging protocols (15, 18). Recently, we described such an MR protocol for the presurgical examination of patients with intractable temporal lobe epilepsy (15). The cornerstone of evaluation is tilted coronal T1-weighted inversion-recovery imaging aimed at showing morphologic hippocampal abnormalities. When the internal hippocampal structure is normal, volumetric measurements may be used to detect subtle asymmetry. Even then, in some patients, the epilepsy is not lateralized with EEG and imaging, and additional testing with invasive EEG monitoring is necessary (13, 17). The decision-making process in the presurgical evaluation of patients with temporal lobe epilepsy must be multiparametric to minimize the risk of an inappropriate operation. For this reason, additional tests, such as a neuropsychological examination, the invasive intracarotid amytal procedure (IAP) (19), and metabolic or functional imaging (PET and SPECT) (17) are nearly always used to corroborate locating results and to give information about language location and memory support.

MR spectroscopy is capable of defining concentrations of some metabolites, such as *N*-acetylaspartate (NAA), creatine (Cr), and choline compounds (Cho) in the brain. Recent studies have shown that NAA, as a marker for neuronal loss (1, 2, 20)(Connelly et al, "1H Spectroscopy...") is often decreased in the afflicted temporal lobe. An increase in both Cho and Cr has also been reported (5–7)(Connelly et al, "1H Spectroscopy..."), although this was not supported by other authors (G. Ende, K. D. Laxer, R. Knowlton, G. Matson, M. W. Weiner, "Quantitative 1H SI Shows Bilateral Metabolite Changes in Patients with Unilateral Temporal lobe epilepsy with and without hippocampal atrophy," In: *Proceedings of the Society of Magnetic Resonance in Medicine,* Nice, France: 1995:144; and C. O. Duc, D. Meier, X. G. Golay, O. M. Weber, H. G. Wieser, P. Boesiger, "Investigation of Temporal Lobe Epilepsy by Quantitative 1H MRS of the Hippocampus In Vivo," In: *Proceedings of the Society of Magnetic Resonance in Medicine,* Nice, France: 1995:1829). Absolute quantification remains difficult, and the NAA/Cho+Cr or NAA/Cr ratios, or the normalized value for NAA, are usually calculated (5–7, 21) (Connelly et al, "1H Spectroscopy"; Achten et al, "Multiparameter..."; Ende et al, "Quantitative..."; Duc et al, "Investigation..."; J. W. Hugg, R. I. Kuzniecky, H. P. Hetherington, et al, "Temporal Lobe Epilepsy Studied by 1HMRSI at 4.1T: Localization before and Follow-up after Surgery," In: *Proceedings of the Society of Magnetic Resonance in Medicine,* Nice, France: 1995:1830; P. Vermathen, G. Ende, K. D. Laxer, et al, "Hippocampal NAA Is Not Reduced in Neocortical Epilepsy: Contrast with Medial Temporal Lobe Epilepsy," in: *Proceedings of the Society of Magnetic Resonance in Medicine,* New York, NY: 1996:138; P. Vainio, K. Partanen, R. Kälviáinen, M. Vapalathi, S. Soimakalio, "1H MRS in Temporal Lobe Epilepsy Patients with Good Seizure Control," in: *Proceedings of the Society of Magnetic Resonance in Medicine,* Nice, France: 1995:1828; W. Van Paesschen, A. Connelly, J. S. Duncan, C. L. Johnson, "Single Voxel 1H Magnetic Resonance Spectroscopy in Patients with MRI-Negative Intractable Temporal Lobe Epilepsy," in: *Proceedings of the Society of Magnetic Resonance in Medicine,* New York, NY: 1996:139). The purpose of our study was to explore further the role of single-voxel proton MR spectroscopy in patients with intractable temporal lobe epilepsy. Several ratios of metabolites and NAA were tested for their value in predicting the side of seizure onset as determined by EEG monitoring and MR imaging.

Materials and Methods

Subjects and Neurologic Assessment

Our study included 12 healthy subjects (age range, 18 to 34 years) and 21 patients with temporal lobe epilepsy (age range, 14 to 53 years) refractory to medical treatment who, at MR imaging, had no neoplastic or traumatic lesions nor any neuronal migration disorder, and whose epilepsy was clearly lateralized with EEG and MR imaging. All patients underwent a clinical neurologic examination, scalp EEG recording, neuropsychological testing, and prolonged video EEG monitoring (Beehive and SZAC 32-channel digital EEG, Telefactor). Habitual complex partial seizures were recorded in all patients (13, 14, 19).

MR Imaging

MR imaging of the temporal lobes was performed on a clinical 1.5-T system. The temporal lobes and hippocampi were evaluated on tilted coronal T1-weighted inversion recovery images, and the volumes of the hippocampus and amygdala were calculated from three-dimensional magnetization prepared rapid gradient-echo images (15).

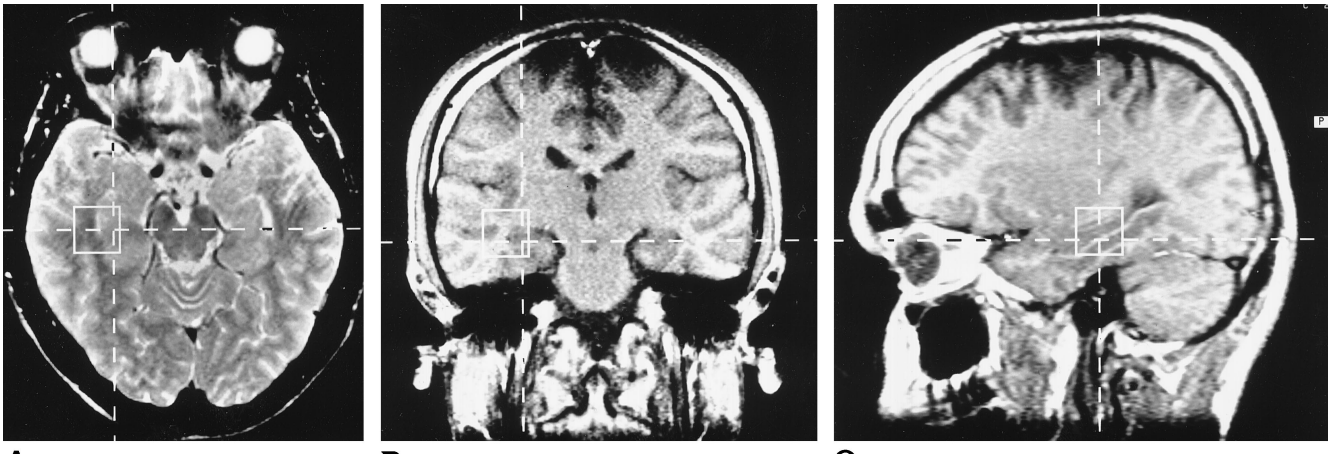

Fig 1. Standard positioning scheme for single-voxel proton MR spectroscopy. This figure shows the standard scheme for positioning of the mesial temporal voxel of 8 mL.

A, Axial T2-weighted (2370/80/1) image shows the voxel positioned at the same level as the brain stem.

B, On coronal half-Fourier T1-weighted (300/15/1) image, care is taken to include half the hippocampus at the medial side.

C, The sagittal half-Fourier T1-weighted (300/15/1) localizer image enables us to stay clear of the tip of the temporal bone to avoid shimming problems. In doing so, partial volume bias due to differences in white and gray matter content in the voxel are minimized

MR Spectroscopy

Single-voxel proton MR spectroscopy was carried out immediately after MR imaging with an 8-mL voxel ($20 \times 20 \times 20$ mm^3) positioned over the mesial temporal lobe, including a part of the hippocampus (Fig 1). This was done for each side. Attention was paid to the reproducibility of the positioning of the voxels with respect to the brain stem and the hippocampus. After positioning of the voxel, the signal over the volume of interest was shimmed to within a linewidth of 3 to 7 Hz. Water suppression was achieved by applying a gaussian 90° pulse on the water frequency followed by a spoiler gradient. Spectra were acquired using a spin-echo sequence with an echo time of 135 milliseconds (22). The repetition time was 1600 milliseconds and the number of excitations was 256. To compensate for eddy current artifacts, we obtained a reference scan with the same sequence parameters but without water suppression and with only eight acquisitions. After correcting for eddy current (23), the time domain spectra were zero filled to 2048 points and a weak gaussian filter with a half-life of 256 milliseconds was applied before fast Fourier transform. The resultant frequency domain spectra required minimal zero- and first-order phase correction, no baseline correction was applied. Three resonances of importance could be identified (Fig 2): NAA at 2 ppm, Cr at 3 ppm, and Cho at 3.2 ppm. These peaks were quantified by simple triangulation. Normalized values for the concentrations of the metabolites were calculated as follows (with the assumption that all spectra had the same number of excitations):

$$(\text{metabolite}) = A_{\text{metabolite}} * \text{VTRA}$$

where $A_{\text{metabolite}}$ is the area under the metabolite peak and VTRA the result from the transmitter adjustment. This normalizes for differences in coil loading (24). Then the metabolite ratios of NAA/Cho+Cr, NAA/Cr, NAA/Cho, and Cho/Cr were calculated. Mean and standard deviations (SD) were calculated for all parameters from the pooled data of the control group.

An asymmetry index for abnormality was defined as the maximum asymmetry value between left and right in the healthy control subjects, but when both left and right temporal lobe values were abnormal, half this value was considered sufficient for tentative lateralization. Thus, five categories of lateralization with the MR spectroscopic parameters were defined, as described in Table 1.

On the basis of the results from clinical data, scalp and video EEG monitoring, and MR imaging, the patients were considered to have either left- or right-sided temporal lobe epilepsy. The value of the different parameters derived from single-voxel proton MR spectroscopy in lateralizing the epileptogenic zone was subsequently tested to support this classification.

An analysis of statistical significance to discriminate populations at the hand of the different parameters was performed using a two-sample *t* test, assuming unequal variances.

Results

Control Subjects

No abnormalities were found on MR images of our control population. Reference values for all the parameters were calculated from the

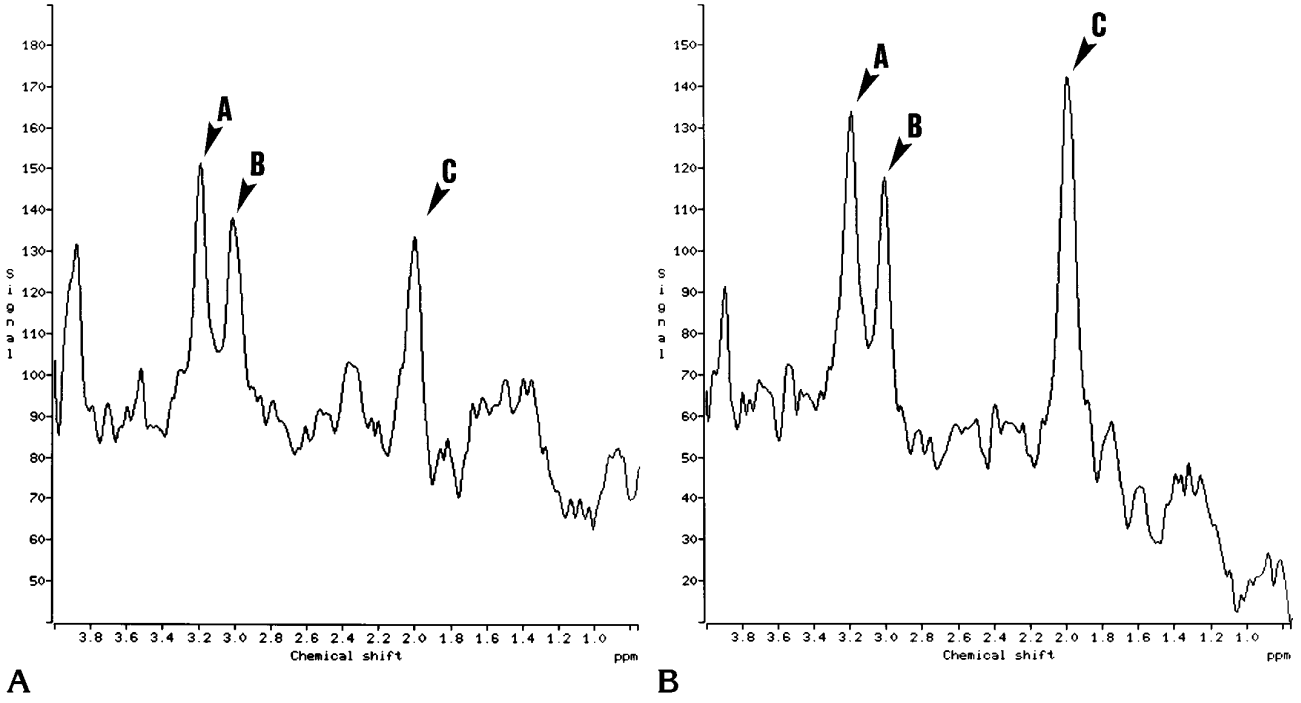

Fig 2. Spectra (1600/135/256) from the left (*A*) and right (*B*) mesial temporal lobes of a patient (case 14) with temporal lobe epilepsy. The three main peaks are, from left to right, Cho at 3.2 ppm (A), Cr at 3 ppm (B), and NAA at 2 ppm (C). It is clear that NAA is lower on the left side in this patient with left-sided temporal lobe epilepsy.

TABLE 1: Categories of lateralization obtained with MR spectroscopic parameters

Category	Label	Explanation
Normal	N	Both values are in the normal range, there is no abnormal asymmetry
Correctly lateralized; clear lateralization	Lat	The ipsilateral value is abnormal, there is a clear abnormal asymmetry*
Bilateral	Bil	Both values are abnormal, there is no asymmetry
Bilateral but lateralized correctly	BilLat	Both values are abnormal, there is a clear abnormal asymmetry on the side predicted by the EEG
Normal but lateralized correctly	Nlat	Both values are in the normal range, but there is a clear abnormal asymmetry
Incorrectly lateralized	W(rong)	The value is worse on the contralateral side, with abnormal asymmetry†

* Ipsilateral refers to the side of EEG abnormalities.
† Contralateral refers to the other side.

pooled values of 22 spectra. Table 2 summarizes these reference values. Two spectra were considered inadequate for evaluation owing to supposed radio-frequency artifacts (the limits were within 2 SD from the mean values). Because of reports from the literature indicating a decrease of NAA and an increase of Cho and possibly Cr in chronic temporal lobe epilepsy, abnormality was defined as below the mean minus 2 SD for NAA/Cho+Cr, NAA/Cr, NAA/Cho, and NAA and as above the mean plus 2 SD for Cho/Cr. In addition, an asymmetry index, defined as the maximum asymmetry in 10 healthy subjects, was defined for each parameter. The asymmetry for a particular parameter was considered abnormal if it exceeded the asymmetry index, except when the values from both temporal lobes were abnormal, in which case the original asymmetry index was divided by two (modified asymmetry index).

Patients

Table 3 describes the various clinical and MR imaging data as well as the categorization for each patient per parameter. The outcome and follow-up after surgery (15 of 21 patients) are also reported (25).

The mean duration of complex partial epilepsy was 21 years (range, 7 to 47 years). The video EEG data showed clear and consistent unilateral seizure onset in all patients, and MR

TABLE 2: Reference values for parameters obtained with single-voxel proton MR spectroscopy

Parameter	NAA/Cho+Cr	NAA/Cr	Cho/Cr	NAA/Cho	NAA
Mean value	0.91	2.04	1.25	1.65	17.1
Standard deviation	0.10	0.23	0.14	0.23	2.50
Minimum	0,73	1,73	0,98	1.27	12.9
Maximum	1,13	2,65	1,54	2.05	22.2
Abnormal if:	<0.71	<1.58	>1.53	<1.19	<12.1
Asymmetry index*	.11 (.05)	.14 (.07)	.13 (.07)	.13 (.07)	.14 (.07)

* When abnormal values for a particular parameter were noted bilaterally, the asymmetry index necessary for lateralization was divided by 2 (modified asymmetry index in parentheses).

TABLE 3: Clinical data, MR imaging results, MR spectroscopic lateralization, and outcome

Patient	Sex	EEG and MR Lateralization	Categorization*					Outcome	Follow-up, m
			NAA/(Cho+Cr)	NAA/Cr	Cho/Cr	NAA/Cho	NAA		
1	F	R	Lat	Lat	NLat	Lat	Lat	1A	18
2	M	R	Bil	N	Bil	Bil	N	1A	18
3	M	R	Lat	NLat	N	NLat	NLat	Recent surgery, no seizures	6
4	F	R	BilLat	BilLat	BilLat	BilLat	N	1A	24
5	F	R	Lat	NLat	NLat	Lat	Lat	Refused surgery	. . .
6	M	R	Lat	N	NLat	Lat	BilLat	Discrepant IAP, not operated on	. . .
7	F	R	Bil	N	Bil	Bil	N	1A	12
8	F	R	Bil	BilLat	N	Bil	Bil	1A	6
9	F	R	BilLat	W	NLat	Lat	BilLat	3A	12
10	F	R	Lat	Lat	N	Lat	Lat	1A	24
11	M	L	BilLat	W	NLat	Lat	Lat	1A	36
12	M	L	Lat	NLat	N	Lat	Lat	Scheduled for surgery	. . .
13	M	L	Lat	Bil	BilLat	Lat	Lat	1A	36
14	M	L	Lat	Lat	W	Lat	Lat	Discrepant IAP, not operated on	. . .
15	M	L	BilLat	Lat	W	Bil	Lat	Recently surgery, no seizures	<6
16	F	L	Lat	Lat	W	Lat	Lat	Invasive EEG: regional onset	. . .
17	M	L	Lat	Lat	Lat	Lat	Lat	1A	24
18	F	L	Lat	Lat	N	N	Lat	3A	12
19	M	L	Lat	Lat	N	NLat	NLat	1A	18
20	F	L	Bil	Bil	N	Bil	BilLat	1A	12
21	M	L	Lat	N	NLat	W	NLat	Discrepant IAP, not operated on	. . .

Note.—IAP indicates intracarotid amytal procedure; 1A, seizure free; and 3A, worthwhile decrease in seizure frequency.

* See Table 1 for definitions.

images showed ipsilateral hippocampal damage in 20 of 21 patients (15). This was depicted on coronal T1-weighted inversion-recovery images as a loss of internal structure (14 of 21), decreased signal (14 of 21), and volume loss (17 of 21). In addition, seven patients had scarring in the white matter of the ipsilateral temporal lobe (15); one patient had ipsilateral severe hippocampal sclerosis and also minimal damage (minimal structural loss) on the contralateral side, this patient was nevertheless included (15); and one patient only had cortical tinning of the left parahippocampal gyrus and scaring of the underlying white matter.

All patients were selected for surgical treatment and 15 of the 21 actually had surgery. Ictal onset zones were confirmed with invasive EEG studies in one patient who had regional rather than focal onset of temporal lobe epilepsy and was considered too much of a risk for surgery. In three patients, the cut-off memory score (six of 11) for the contralateral hippocampus on the IAP was not attained (discrepant IAP), and surgery was contraindicated. One patient with temporal lobe epilepsy refused surgery and one is scheduled to be operated on in the near future. However, these six patients fulfilled all the other inclusion criteria.

Clear concordant lateralization (labeled "Lat") was best achieved with NAA/Cho+Cr followed by NAA and NAA/Cho. Only NAA and NAA/Cho+Cr showed no discordant lateralization (Table 4). When the categories "Nlat" (both values in the normal range, but a clear abnor-

mal asymmetry) and "BilLat" (both values abnormal, with no asymmetry) were also considered lateralizing, then epilepsy was lateralized correctly by means of NAA/Cho+Cr or NAA in 17 (81%) of our 21 patients. Even then, with the lower requirements for asymmetry, there was no false lateralization with either of these two parameters. Bilateral abnormalities without abnormal asymmetry were present in four subjects by means of NAA/Cho+Cr and only in one by means of NAA parameters. With NAA, three patients had normal values in both temporal lobes, without asymmetry. This was never the case for NAA/Cho+Cr.

NAA/Cr and NAA/Cho both performed less well than NAA/Cho+Cr and NAA in predicting the side of epilepsy: only 13 and 14 patients, respectively, had their epilepsy lateralized correctly with these ratios. However, with the use of NAA/Cr in two patients and NAA/Cho in one patient, epilepsy was lateralized to the contralateral side.

The ratio Cho/Cr performed worst of all. Seven patients had symmetric normal values and three had epilepsy lateralized to the contralateral side. This is not surprising, since at least one report (9) mentions a trend toward increases in both Cho and Cr in the epileptic temporal lobe.

In our series, the ratios NAA/Cho+Cr, NAA/Cr, NAA/Cho, and NAA showed a statistically significant difference between ipsilateral and contralateral sides, and also between the ipsilateral side and normal values and between the contralateral side and normal values ($\alpha = .01$). This indicates an important statistical bilateral involvement of the temporal lobes, as has been described by others (18, 24, 25). We found no statistically significant difference for Cr or Cho, but a clear trend toward higher ipsilateral Cho and lower bilateral Cr values was evident (Table 5).

As proposed by Ende et al ("Quantitative..."), the combination of NAA and NAA/Cho+Cr shows a clear trend when the data pairs of the contralateral temporal lobe are connected with the ipsilateral data pairs (solid connecting lines in Fig 3). Only three subjects did not exhibit this trend, but their epilepsy was not lateralized by our criteria. Nevertheless, this did not yield additional lateralizing information in our series.

TABLE 4: Categorization of the TLE patient with different MR spectroscopic parameters

Category	NAA/Cho+Cr	NAA/Cr	Cho/Cr	NAA/Cho	NAA
N	0	4	7	1	3
Nlat	0	3	6	2	3
Lat	13	8	1	11	11
BilLat	4	2	2	1	3
Bil	4	2	2	5	1
W(rong)	0	2	3	1	0

Discussion

Our study addresses the issue of which parameter from single-voxel proton MR spectroscopy can best be used to lateralize temporal lobe epilepsy refractory to medical treatment before surgery, and how its use can be optimized. Although there is a trend toward the use of chemical-shift imaging for this purpose (3, 11, 12)(Ende et al, "Quantitative..."; Duc et al, "Investigation..."; Hugg et al, "Temporal Lobe..."; Vermathen et al, "Hippocampal..."), our choice to use single-voxel proton MR spectroscopy for this study of patients with temporal lobe epilepsy was made when our epilepsy program was established in 1991. At that time, chemical-shift imaging was in its infancy and outside the capability of our scanner. Furthermore, it is important to note that pathologic

TABLE 5: Statistical analysis

Parameter	NAA/Cho+Cr	NAA/Cr	NAA/Cho	Cho/Cr	NAA	Cr	Cho
Average normal value	0.91	2.04	1.65	1.25	17.1	8.46	10.54
Standard deviation of normal	0.10	0.23	0.23	0.14	2.50	1.49	2.28
Average ipsilateral value	0.60	1.46	1.03	1.43	11.69	7.99	11.44
Standard deviation of ipsilateral	0.09	0.27	0.18	0.24	2.99	1.31	2.56
Average contralateral value	0.78	1.84	1.38	1.37	14.34	7.92	10.67
Standard deviation of contralateral	0.13	0.37	0.28	0.30	2.92	1.55	2.53
P value I/C	<.0001	.0002	<.0001	.21	.003	.43	.17
P value I/N	<.0001	<.0001	<.0001	.002	<.0001	.14	.11
P value C/N	.0005	.02	<.0005	.05	.001	.12	.43

Note.—I/C indicates ipsilateral versus contralateral; I/N, ipsilateral versus normal; C/N, contralateral versus normal.

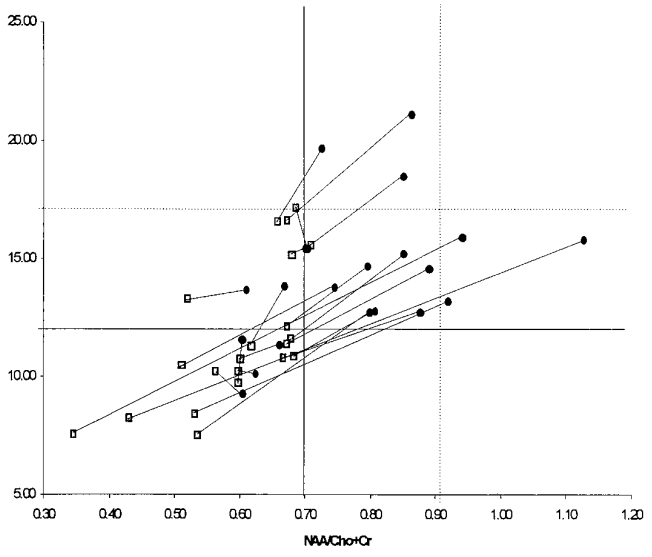

Fig 3. NAA over NAA/Cho+Cr plot with the paired data values (*connecting lines*) of the ipsilateral (*squares*) and contralateral (*circles*) temporal lobes for each patient. The *connecting lines* are at the mean (*dashed*) and 2 SD below the mean (*solid*) for NAA (*horizontal lines*) and for NAA/Cho+Cr (*vertical lines*). A clear trend can be discerned in the data pairs from the contralateral toward the ipsilateral side. Only three subjects did not conform to this trend, but their epilepsy was not lateralized by our criteria.

studies have shown that abnormalities such as neuronal loss and astrocytic reactions often extend beyond the hippocampus (26, 27). This is supported further by interictal PET studies in which decreased metabolism is found in large areas of the afflicted temporal lobes (16).

Because of possible bias due to different concentrations of the metabolites in the hippocampus and the neocortical gray matter and white matter (20), a standard positioning scheme was adopted from the beginning to diminish the effects of partial volume differences in the chosen voxels (28). Because the quality of the spectra depends largely on adequate shim values within the voxel, care was taken to stay clear of the temporal bone. This standard positioning scheme is depicted in Figure 1 and the benefits of using such standardization are demonstrated by good quality spectra and by the low SD for the normal values.

That no attempt has been made to calculate absolute concentration of the metabolites rather than normalized values is due to the lack of fully relaxed water spectra and the omission of the use of an external reference. Furthermore, it is clear from the literature and from our study that use of an internal reference with point-resolved spectra at 135 milliseconds is excluded because alterations of all the visible metabolites have been reported (1, 4, 5–7, 20)(Connelly et al, "1H Spectroscopy..."; Ende et al, "Quantitative..."; Duc et al, "Investigation..."). Moreover, possible changes in the relaxation times have to be taken into account.

Because of the aforementioned difficulties encountered in calculating absolute concentrations (especially in the temporal lobe), some metabolite ratios, such as NAA/Cho+Cr or NAA/Cr (or Cr/NAA), or the normalized value of the metabolite concentrations are usually calculated (5–7)(Connelly et al, "1H Spectroscopy..."; Achten et al, "Multiparameter..."; Ende et al, "Quantitative..."; Vermathen et al, "Hippocampal..."). In some studies, though, the absolute concentrations were calculated nevertheless (10)(Ende et al, "Quantitative..."; Duc et al, "Investigation..."; Vermathen et al, "Hippocampal..."; Vainio et al, "1H MRS..."). Several reports (1, 2, 5–7, 20)(Connelly et al, "1H Spectroscopy..."; Ende et al, "Quantitative..."; Duc et al, "Investigation...") have indicated a lower NAA, a higher or unchanged Cho, and a variable Cr; and thus the ratios of NAA/Cho+Cr, NAA/Cr, NAA/Cho, and Cho/Cr have been tested for their ability to lateralize temporal lobe epilepsy. We further tested a normalized concentration of NAA as a lateralizing parameter. Only recently have other studies been reported in which more than one parameter was taken into account (Ende et al, "Quantitative..."; Vermathen et al, "Hippocampal..."). Each of these studies used chemical-shift imaging and found that concordant lateralization was also best with NAA and NAA/Cho+Cr.

In our study, clear lateralization to the ipsilateral side as predicted by EEG and MR imaging, with an abnormal parameter on the ipsilateral side only, was accomplished best with NAA/Cho+Cr (in 13, or 62%, of 21 patients). This is in agreement with several previous studies in which the single-voxel proton MR spectroscopic technique was used (5, 6, 10)(Connelly et al, "1H Spectroscopy..."). The additional use of an asymmetry index for lateralization purposes on an individual basis was proposed by Vainio et al (10). Using NAA from single-voxel proton MR spectroscopic examinations, these authors reported good seizure control after temporal lobectomy in patients with an asymmetry index of more than 0.10. Others (18)(Van Paesschen et al, "Single Voxel...") have proposed the use of a lowered asymmetry index of 0.05 for the further

lateralization of epilepsy in subjects with bilaterally low NAA/Cho+Cr at single-voxel proton MR spectroscopy. We defined the abnormal asymmetry as the highest value found in healthy subjects for a particular parameter; however, in the instance of bilateral abnormal values, this value was divided by two. For NAA/Cho+Cr, the same value as proposed by Jackson et al (7) was found. This resulted in additional correct lateralization in four patients with the use of NAA/Cho+Cr and in three patients with the use of NAA. Thus, no erroneous lateralization occurred. Abnormal asymmetry in the presence of normal values was also considered lateralizing; but in that situation, the asymmetry index must be higher than the maximum value found in healthy subjects. This was the case for three patients with NAA. With this modified definition of asymmetry, NAA/Cho+Cr and NAA scored equally well and lateralization could be achieved in 17 (81%) of the 21 patients. Because no false lateralization occurred with this definition of asymmetry, we believe that such use of the asymmetry index may be a way out of too many bilateral normal or abnormal values.

The eventual usefulness of an asymmetry index as we have defined it needs to be confirmed in larger groups of prospectively studied patients with temporal lobe epilepsy. Whereas our study addressed only patients in whom epilepsy was easy to lateralize with EEG and MR imaging, many cases of temporal lobe epilepsy are more difficult to lateralize because of inconsistent findings on different presurgical tests. Such patients then need to go on to invasive EEG procedures for lateralization (19, 26). It is for these patients that we seek the use of single-voxel proton MR spectroscopy to yield the extra information that can spare them the invasive monitoring.

Because there is evidence of a high percentage of bilateral abnormalities (26, 27), it is not surprising that in eight of our 21 patients a bilateral low NAA/Cho+Cr ratio was found. This is also in good agreement with previous studies in which this ratio has been used (5–7)(Connelly et al, "1H Spectroscopy..."; Achten et al, "Multiparameter..."). This is further supported by our statistical analysis, in which a significant population difference exists (at $\alpha = .01$) between the pooled values of NAA and NAA/Cho+Cr in the temporal lobes of healthy subjects and that of either the ipsilateral or the contralateral temporal lobe of patients.

Unlike several other studies in which single-voxel proton MR spectroscopy was used for patients with temporal lobe epilepsy (5–7)(Connelly et al, "1H Spectroscopy..."), our results indicate a trend toward a lower Cr in both temporal lobes. This is more in accordance with a recent chemical-shift imaging study (Duc et al, "Investigation...") that also found a lower Cr, but more pronounced on the ipsilateral side. On the other hand, a slightly higher Cho was found on the ipsilateral side only. We speculate that this higher Cho may be related to unexplained changes in the visibility of phosphatidylcholine or other choline compounds that may be related to epileptogenesis (30).

The fewer bilateral abnormalities found with NAA (in only three of eight patients with bilateral low NAA/Cho+Cr) may point to the importance of a higher Cho in some subjects with normal or nearly normal NAA.

As stressed earlier, the definition of an adequate asymmetry index for our patients opens the possibility for further lateralization of epilepsy in subjects with bilateral abnormalities. On the other hand, the presence of symmetric, bilateral, abnormal NAA/Cho+Cr ratios does not mean that such patients cannot be operated on without success. In fact, all four of our patients who had such abnormalities were operated on successfully and had no recurrent seizures. One of these was the patient with bilateral, symmetric low NAA. Of the four patients classified as "BilLat" with NAA/Cho+Cr, three are seizure-free after surgery and one has had a significant decrease in seizure frequency. Of the 15 patients who had surgery, only one has had recurrent attacks, and this patient was categorized as "Lat" by both NAA and NAA/Cho+Cr.

In summary, the use of an asymmetry index improved the lateralizing capacity of the parameters NAA/Cho+Cr and NAA derived from the mesial temporal lobes of patients with unilateral temporal lobe epilepsy by means of single-voxel proton MR spectroscopy. Frequent bilateral temporal lobe involvement was found, asymmetrically for NAA and Cho and symmetrically for Cr.

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