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¹H MRSI predicts surgical outcome in MRI-negative temporal lobe epilepsy

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Abstract

¹H MRS imaging (MRSI) was performed on 15 patients with MRI-negative temporal lobe epilepsy (TLE) who underwent seizure surgery. The non—seizure-free patients (NSF) ipsilateral hippocampal *N*-acetylaspartate (NAA)/(Cr+Cho) *z* scores were lower than the contralateral scores ($p = 0.04$), and the NSF ipsilateral *z* scores were lower than the seizure-free patients' (SF) ipsilateral *z* scores ($p = 0.0049$). Similarly, NSF contralateral scores were lower than contralateral SF ($p = 0.02$). These findings suggest NAA predicts the surgical outcome in patients with TLE without evidence of mesial temporal sclerosis on MRI.

Patients with temporal lobe epilepsy (TLE) frequently have evidence of mesial temporal sclerosis (MTS) on MRI (increased hippocampal T2 signal or hippocampal atrophy). These patients have a high probability (>90%) of becoming seizure free after surgery.¹ However, 20 to 30% of patients with TLE demonstrate no MRI abnormalities and only 50% of these patients become seizure free after surgery.¹ ¹H MRS imaging (MRSI) measures a number of metabolites, including *N*-acetyl aspartate (NAA), a marker of neuron viability and density.² ¹H MRSI has shown NAA is reduced in the epileptogenic hippocampus,^{3–5} frequently even when the MRI is normal,³ suggesting NAA can help identify the seizure focus. Previous studies suggested ¹H MRSI may predict surgical outcome, but most of these subjects had MTS on MRI.^{7,8} The ability of MRSI to predict surgical outcome has not been firmly established and its efficacy in predicting surgical outcome in MRI-negative patients has never been demonstrated.

Methods

After informed consent, ¹H MRSI of the hippocampus was obtained preoperatively from 15 patients with MRI-negative TLE.⁵ The patients represent all the patients with TLE with normal MRI who were operated on at the University of California, San Francisco, from 1994 to 1999. Data were also obtained from 28 control subjects. All patients had an extensive presurgical evaluation and underwent high-resolution MRI and hippocampal voluming to establish the

normal MRI classification. The patients subsequently underwent temporal lobectomies on the side localized by the ictal EEG. The ^1H MRSI results were not used in the surgical planning.

Although the ^1H MRSI acquisition technique was the same for all patients and control subjects, over the course of this study the hippocampal spectra were processed by two different methods. Spectra from 10 patients and 16 control subjects were processed using Siemens LUISE software (Iselin, NJ),⁵ whereas spectra from five patients and 12 control subjects were processed using the FITT program.⁶ In order to combine these results, standardized z scores were generated for each patient by comparing their NAA ratios with their contemporaneous normal control subjects. Based on their outcome (minimum follow-up, 2 years; mean, 5.3 years), patients were divided into seizure-free (SF) and not—seizure-free (NSF) groups. Fluorodeoxy-glucose PET scans did not provide any additional information. Similarly, the pathology was the same for SF and NSF, consisting of either nonspecific gliosis or MTS. The hypothesis tested was the ability of ^1H MRSI to predict surgical outcome. Two-tailed unpaired Student's t -test analysis was used to determine the significance of the differences between z scores. A two-tailed χ^2 test was used for the categorical analysis.

Results

Table 1 shows the z scores obtained from the ipsilateral and contralateral hippocampi for the patients. In SF patients, the ipsilateral and contralateral z scores were similar to control subjects and to each other (ipsilateral -0.6 ± 1.6 , contralateral -0.08 ± 1.2). In contrast, the ipsilateral z scores of NSF patients were lower than the contralateral scores (-2.7 ± 0.7 vs -1.7 ± 1.1 , $p = 0.04$). The ipsilateral z scores of NSF patients were lower than the ipsilateral z scores of SF patients (-2.7 ± 0.7 vs -0.6 ± 1.6 , $p = 0.0049$). Similarly, the contralateral z scores of NSF patients were also lower than the contralateral z scores of SF patients (-1.7 ± 1.1 vs -0.08 ± 1.2 , $p = 0.02$). Table 2 shows the outcome of patients with z scores that fell above and below an arbitrarily chosen z score value of -1.5 (an approximate p value of 0.06). There was a clear discrimination between the ipsilateral hippocampi of SF and NSF patients ($p = 0.003$). The contralateral hippocampi were also different ($p = 0.03$).

The figure displays the ipsilateral vs contralateral z scores for the patients. Only four of nine SF subjects were lateralized by having ipsilateral z scores lower than the contralateral side. The other SF patients had contralateral scores lower than their ipsilateral scores. In contrast, all but one NSF patient were lateralized with ipsilateral z scores less than contralateral z scores.

Discussion

This study shows that in TLE subjects with normal MRI, the NAA ratio predicted surgical response. The ratios of SF patients were higher and closer to control values than patients with poor outcomes. We interpret this finding to mean that patients who do not have severe hippocampal disease, whether ipsilateral or contralateral, are more likely to respond to surgery. A second and unexpected finding was that patients who were lateralized by NAA ratios (i.e., smaller ipsilateral ratios compared with the contralateral hippocampus) had worse surgical outcomes than poorly lateralized patients.

It has been previously reported in TLE that the preoperative ipsilateral NAA had no predictive value, but contralateral NAA correlated with seizure outcome.⁷ Those patients with decreased contralateral NAA had poorer surgical outcomes than patients with normal contralateral NAA. However, these patients had lateralizing MRI scans. Our results confirm this finding for MRI-negative patients, showing lower contralateral z scores for patients that were not seizure free and extending this finding to the ipsilateral side as well. These results suggest that subjects with substantial metabolic abnormalities, especially in the contralateral hippocampus, may

have seizure foci that extend beyond the ipsilateral hippocampus. In this case, removal of the ipsilateral hippocampus would be less likely to eliminate seizures.

The second finding was that patients who were “well lateralized” by NAA (i.e., ipsilateral NAA ratios lower than contralateral ratios) had worse surgical outcomes than patients who were “poorly lateralized.” This finding was completely unexpected. Many studies from this laboratory and others^{3,4} have shown that decreased NAA can be used to lateralize patients with TLE. We also reported several years ago that hippocampal atrophy was not necessary for lateralization with NAA.³ Patients who are well lateralized have been considered to be better surgical candidates than patients who are poorly lateralized (i.e., ipsilateral NAA equal to or greater than the contralateral NAA). Based on this assumption, a number of groups have reported using hippocampal lateralization by ¹H MRSI as part of their presurgical planning. Therefore, our a priori expectation was that patients who were lateralized by MRSI would have better surgical outcomes. We also expected that patients who did not lateralize would have lower contralateral NAA ratios, suggesting contralateral disease. In patients with TLE with bilateral hippocampal atrophy, concordant NAA/Cr asymmetry was associated with favorable surgical outcome.⁸ Contrary to expectations, many of our patients with good surgical outcomes were not lateralized (5/9) and many of the patients with poor outcomes were well lateralized (5/6). Based on these results, we believe that the extent of lateralization or asymmetry of the NAA ratio should not be used for the clinical presurgical assessment of patients with TLE, at least in patients without evidence of MTS on MRI. It should be emphasized that these results were obtained in only 15 subjects and should be replicated with a larger sample size. However, our results do support the use of the ipsilateral and contralateral NAA ratios for prediction of surgical response in this MRI-negative group.

A possible explanation for the poor correlation between lateralization with NAA and surgical outcome is that patients with normal MRI TLE may represent a different syndrome than TLE with hippocampal atrophy. Patients with TLE with normal MRI scans (compared with MTS) tend to have different natural histories (older age at onset, later age at CNS insult), different etiologies (less often febrile seizures, more often a history of meningitis), and different pathologies (frequently normal histology, or the unusual finding of end folium sclerosis).^{9,10} In the absence of substantial cell loss, NAA would be expected to be less abnormal, as was found in this study.

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References

1. Garcia PA, Laxer KD, Barbaro NM, Dillon WP. Prognostic value of qualitative magnetic resonance imaging hippocampal abnormalities in patients undergoing temporal lobectomy for medically refractory seizures. *Epilepsia* 1994;35:520–524. [PubMed: 8026397]
2. Urenjak J, Williams SR, Gadian DG, Noble M. Specific expression of N-acetylaspartate in neurons, oligodendrocyte-type-2 astrocyte progenitors, and immature oligodendrocytes in vitro. *J Neurochem* 1992;59:55–61. [PubMed: 1613513]
3. Knowlton RC, Laxer KD, Ende G, et al. Presurgical multimodality neuroimaging in EEG lateralized temporal lobe epilepsy. *Ann Neurol* 1997;42:829–837. [PubMed: 9403474]
4. Cendes F, Andermann F, Preul MC, et al. Lateralization of temporal lobe epilepsy based on regional metabolic abnormalities in proton magnetic resonance spectroscopic images. *Ann Neurol* 1994;35:211–216. [PubMed: 8109901]
5. Vermathen P, Ende G, Laxer KD, et al. Hippocampal N-Acetylaspartate in neocortical epilepsy and mesial temporal lobe epilepsy. *Ann Neurol* 1997;42:194–199. [PubMed: 9266729]

6. Soher BJ, Young K, Govindaraju V, Maudsley AA. Automated spectral analysis III: application to in vivo proton MR spectroscopy and spectroscopic imaging. *Magn Reson Med* 1998;40:822–831. [PubMed: 9840826]
7. Kuzniecky R, Hugg J, Hetherington H, et al. Predictive value of 1H MRSI for outcome in temporal lobectomy. *Neurology* 1999;53:694–698. [PubMed: 10489028]
8. Li LM, Cendes F, Antel SB, et al. Prognostic value of proton magnetic resonance spectroscopic imaging for surgical outcome in patients with intractable temporal lobe epilepsy and bilateral hippocampal atrophy. *Ann Neurol* 2000;47:195–200. [PubMed: 10665490]
9. Engel JJ. Introduction to temporal lobe epilepsy. *Epilepsy Res* 1996;26:141–150. [PubMed: 8985696]
10. Stefan H, Feichtinger M, Pauli E, et al. Magnetic resonance spectroscopy and histopathological findings in temporal lobe epilepsy. *Epilepsia* 2001;42:41–46. [PubMed: 11207783]

Figure. Ipsilateral (ipsi) vs contralateral (contra) NAA/(Cr+Cho) ratio z scores of seizure-free (A) and not seizure-free (B) patients with temporal lobe epilepsy.

Table 1

*Hippocampal NAA/(Cr+Cho) ratio z scores** of ipsilateral (ipsi) and contralateral (contra) side in patients with temporal lobe epilepsy with normal MRI

Patient no	Sex	Age at onset, y	Seizure duration, y	Ipsi z	Contra z
Seizure free					
1	F	12	7	2.4	0.3
2	F	38	7	0.1	-0.6
3	F	36	19	0.0	-0.2
4	F	21	24	-0.3	-1.9
5	F	29	1	-0.4	-1.0
6	F	12	31	-0.5	1.2
7	M	32	5	-1.4	-0.7
8	F	5	19	-2.6	2.1
9	F	3	46	-2.8	0.1
Mean $\pm$ SD		19 $\pm$ 17	17 $\pm$ 10	-0.6 $\pm$ 1.6	-0.08 $\pm$ 1.2
Not seizure free					
10	F	5	21	-1.9	-0.8
11	M	40	3	-2.1	-1.5
12	F	2	31	-2.2	-1.7
13	F	30	11	-2.8	-3.0
14	M	33	11	-3.4	-0.2
15	M	3	24	-3.5	-2.8
Mean $\pm$ SD		21 $\pm$ 13	18 $\pm$ 14	-2.7 $\pm$ 0.7	-1.7 $\pm$ 1.1
t-Test [†]				0.0049	0.02

* Ratio z score = (individual patient — average of controls)/SD of controls. The average for the initial control group was 0.81 $\pm$ 0.06 (range 0.68 to 0.91) and the second group of controls 0.83 $\pm$ 0.13 (range 0.69 to 1.09).

[†]Two-tailed unpaired t-test of seizure free vs not seizure free.

Table 2

Number of patients above and below a z score of -1.5 for ipsilateral (ipsi) and contralateral (contra) hippocampus

Class	z Score > -1.5	z Score ≤ -1.5
Ipsi [*]		
Seizure free	7	2
Not seizure free	0	6
Contra [†]		
Seizure free	8	1
Not seizure free	2	4

^{*} $p < 0.003$, two-tailed χ^2 .

[†] $p < 0.03$, two-tailed χ^2 .