

## MRI and <sup>1</sup>H-MRS detects volumetric and metabolic abnormalities of hippocampal sclerosis in temporal lobe epilepsy

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### Abstract

**Objective:**To further investigate the ability of MRI and <sup>1</sup>H-MRS techniques for presurgical evaluation of hippocampal sclerosis. **Methods:**MRI and <sup>1</sup>H-MRS were performed on 30 healthy subjects to determine the confidence levels. Eight patients who were pathologically confirmed hippocampal sclerosis were then studied using the same protocols. The difference of hippocampal formation (DHF) was used to determine atrophy of hippocampus. Areas under the peak of N-acetylaspartate(NAA), Creatine(Cr) and Choline (Cho) were measured, and the ratios of NAA/Cr, Cho/Cr, and NAA/Cr+Cho were calculated. NAA/Cr+Cho value was applied to localize the seizure focus. **Results:**Two patients showed hippocampal atrophy according to DHF value. NAA/Cr ratio decreased significantly in ipsilateral hippocampus compared to that in contralateral hippocampus and control subjects ( $P < 0.01$ ). Cho/Cr value increased in both ipsi- and contralateral hippocampus in comparison with that in control subjects ( $P < 0.01$ ). NAA/Cr+Cho ratio, however, significantly reduced in both ipsi- and contralateral hippocampus ( $P < 0.01$ ) with lowest NAA/Cr+Cho ratio in seizure foci. Six patients could be lateralized by reduced and/or asymmetric NAA/Cr+Cho value. **Conclusion:**<sup>1</sup>H-MRS should be a promising diagnostic tool to detect neuron abnormality. <sup>1</sup>H-MRS and MRI complement each other in presurgical lateralization of epileptogenic lesion in epilepsy patients.

**Keywords:** hippocampal sclerosis; proton magnetic resonance spectroscopy; magnetic resonance image

### INTRODUCTION

The most common lesion in refractory temporal lobe epilepsy (TLE) is Hippocampal sclerosis (HS). Surgical resection of the hippocampus and anterior temporal lobe can cure epilepsy in most patients<sup>[1,2]</sup>. To achieve good surgical outcomes, the accurate preoperative lateralizing and localization of the epileptogenic focus is therefore essential. Several reports have described that MR imaging demonstrated atrophy and/or a high T2 signal in the affected hippocampus. But in many cases it reveals no abnormalities<sup>[3,4]</sup>. Proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) is a noninvasive technique to detect cerebral metabolic abnormality. Studies have shown that decreased NAA/Cr ratio correlated with neuronal loss and/or gliosis in seizure foci<sup>[5,6]</sup>. However,

there were no consistent metabolic abnormalities in the contralateral hippocampus. The purpose of our study is to further investigate the ability of MRI and <sup>1</sup>H-MRS techniques for presurgical evaluation of TLE patients.

### MATERIALS AND METHODS

#### Subjects

Control subjects included 30 healthy subjects with no history of seizures or other neurological abnormalities (16 men and 14 women). Mean age at examination was  $26 \pm 8$  years old. Ninety-five percent confidence levels of MRI and MRS data were derived from control subjects.

Eight patients with refractory TLE were investigated (5 men and 3 women). Mean age at examination was  $20 \pm 6$  years old. Seizure duration ranged from 2 to 20 years with an average of 11 years. The seizure foci were lateralized by multiple surface interictal EEGs and video-

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monitoring EEGs. All patients underwent surgical resection of the epileptogenic temporal lobe to control their refractory seizure.

### MRI and MRS examinations

MRI and MRS were performed on a 2.0 Tesla Gyrex SGR MR system. All subjects had both MRI and  $^1\text{H}$ -MRS examinations using the same protocols.

MRI: Axial images, fast spin echo TR/TE=4000/96ms, slice thickness = 5 mm, interslice gap = 1 mm. Tilted coronal images(perpendicular to the long axis of the hippocampus). Spin echo TR/TE = 500/12 ms, slice thickness = 4 mm, interslice gap = 1mm. The volume of hippocampal was measured manually by contouring the boundary of hippocampus formation from tilted coronal images. The difference of hippocampal formation(DHF) was calculated by right hippocampus volume minus left hippocampus volume.

$^1\text{H}$ -MRS: Single voxel  $^1\text{H}$ -MRS was carried out using point resolved spectroscopy sequence(PRESS) with TR = 2 000 ms, TE = 135 ms, and times of excitation = 200. Spectra were obtained from both hippocampal areas separately. Volumes of interest(VOIs) = 1.5 cm × 2.4 cm × 2.0 cm. VOI was carefully placed to avoid contamination from petrous fat, skull base and sphenoid sinus(**Fig 1**). Local shimming and water suppression pulse were employed before the spectra acquisition. The time domain data were corrected for eddy-current induced phase modulation using non-water-suppressed data as reference. The signal from NAA (2.0 ppm), Cr (3.0 ppm) and Cho(3.2 ppm) were quantified by integration of the peak areas. The metabolite ratio of NAA/Cr+Cho, NAA/Cr and Cho/Cr were then calculated.



Cuboid VOI had to be placed carefully to avoid the petrous fat, skull base and sphenoid sinus.

**Fig 1** Axial T2-weighted image showed the position of VOI for  $^1\text{H}$ -MRS acquisition

### Statistical analysis

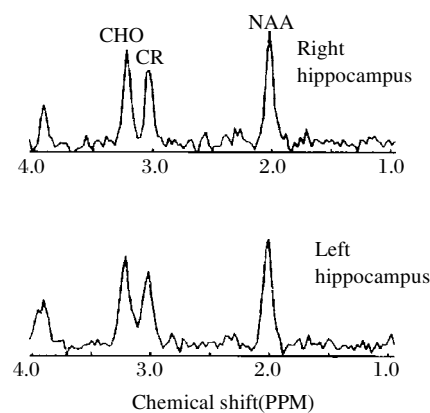
Ninety-five percent confidence levels of DHF and NAA/Cr+Cho from control subjects were used as threshold values to determine hippocampal volumetric and metabolic abnormality in patients. Statistical significance of

NAA/Cr+Cho and Cho/Cr between control and patient groups was assessed using the Student *t* test.

## RESULTS

### Control subjects

MRI studies showed that the value of DHF was  $0.11 \pm 0.15$ (mean  $\pm$  SD), and the 95% confidence level was -0.19 to 0.41. MRS studies demonstrated that the signal from NAA was greater than those from Cr and Cho(**Fig 2**). And the peaks from both hippocampi were symmetrical in all control subjects. The mean values of NAA/Cr+Cho, NAA/Cr and Cho/Cr were  $0.74 \pm 0.07$ ,  $1.58 \pm 0.06$  and  $1.06 \pm 0.06$  respectively. The lower limit of 95% confidence level of NAA/Cr+Cho was 0.60, and the difference of NAA/Cr+Cho between two hippocampi within same subject was less than 0.07.

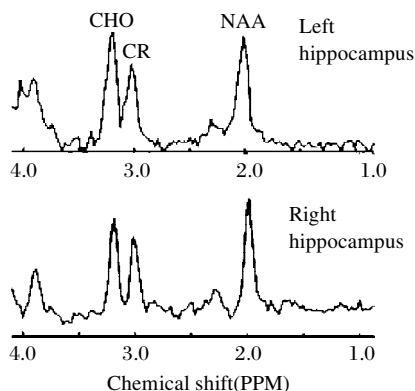


The difference of NAA/Cr+Cho within same subject was less than 0.07. The ratios were 0.70 and 0.67 for right and left hippocampus respectively in this subject.

**Fig 2**  $^1\text{H}$ -MRS from right and left hippocampus in a normal subject

### TLE patients

According to the 95% confidence level of DHF, two out of 8 patients showed unilateral hippocampal atrophy and the lateralization was concordant with video-monitoring EEGs results(patient No 2,5). MRS study showed that NAA peak from ipsilateral side was lower than that from contralateral side in the patients(**Fig 3**). On the basis of 95% confidence level of NAA/Cr+Cho, three patients demonstrated unilateral decreased NAA/Cr+Cho(patient No 2,7,8). Out of five patients who had bilateral decreased NAA/Cr+Cho, three showed lower NAA/Cr+Cho on ipsilateral hippocampus at least by 0.07 compared with that on contralateral side(patient No 1, 3, 6). The other two cases could not be lateralized because both temporal lobes showed severe abnormalities in NAA/Cr+Cho ratio(patient No 4,5), but one of them could be lateralized by DHF value(patient No 5)(**Tab 1**).



Spectra from a TLE patient with spike in left temporal lobe. NAA signal from left hippocampus was significantly decreased, and the NAA/Cr+Cho ratios were 0.60 and 0.78 in left and right hippocampus respectively. Histological findings showed neuron loss and glial hyperplasia in left temporal lobe.

**Fig 3** <sup>1</sup>H-MRS from right and left hippocampus in a TLE patient.

NAA/Cr+Cho ratio significantly reduced in both ipsi- and contralateral hippocampus ( $P < 0.01$ ), with even lower value in seizure foci ( $P < 0.05$ ). NAA/Cr ratio decreased significantly in ipsilateral hippocampus compared to that in contralateral side and control subjects ( $P < 0.01$ ). Cho/Cr value, however, increased in both ipsi- and contralateral hippocampus compare with that in control subjects ( $P < 0.01$ ) (**Tab 2**). The focal NAA/Cr+Cho and NAA/Cr reduction combined with Cho/Cr increase were consistent with pathology findings of neuron loss and gliosis in the surgical resected epileptogenic foci.

## DISCUSSION

Although most TLE patients showed no abnormalities in anatomical study, MRI is a useful technique to detect atrophy and/or a high T2 signal in HS. Measurement of hippocampal volume could improve the sensi-

**Tab 1** The clinical information of patients from EEG, MRI, <sup>1</sup>H-MRS and pathology findings

NO	Sex/Age	Duration(year)	Seizure Type	EEG	DHF	NAA/Cr+Cho		Pathology findings
						ipsi	contra	
1	F/16	2	Global	Right	- 0.13	0.50	0.60	Neuron loss and glial hyperplasia
2	F/23	10	Complex+Partial	Left	0.92	0.60	0.78	Neuron loss and glial hyperplasia
3	M/18	15	Partial+Global	Bitemp+R	- 0.05	0.50	0.57	Neuron loss and glial hyperplasia
4	F/26	20	Complex+Partial	Bitemp+R	0.18	0.53	0.50	Neuron loss and glial hyperplasia
5	M/15	7	Complex +Partial	Bitemp	- 0.69	0.60	0.56	Neuron loss
6	M/26	6	Complex +Partial	Left	0.17	0.40	0.60	Neuron loss and glial hyperplasia
7	M/13	11	Partial+Global	Bitemp+R	- 0.02	0.50	0.75	Glial hyperplasia
8	M/25	14	Complex+Partial	Right	- 0.01	0.59	0.75	Glial hyperplasia

**Tab 2** Ratios of NAA/Cr+Cho, NAA/Cr and Cho/Cr from control subjects and TLE patients

	Metabolic values			Statistic comparisons(P value)		
	ipsi-	contra-	controls	ipsi-contra	ipsi-control	contra-control
NAA/Cr+Cho	0.55 ± 0.04	0.63 ± 0.02	0.77 ± 0.03	<0.05	<0.01	<0.01
NAA/Cr	1.17 ± 0.08	1.52 ± 0.09	1.58 ± 0.06	<0.01	<0.01	0.56
Cho/Cr	1.38 ± 0.08	1.42 ± 0.10	1.06 ± 0.06	0.26	<0.01	<0.01

tivity of MRI detection of HS<sup>[7,8]</sup>. DHF is a practical method to measure the hippocampal volume since there is no need to correct for skull size. According to DHF threshold, two out of eight patients demonstrated unilateral hippocampal atrophy and the seizure foci could be correctly lateralized. DHF in other six patients fit in normal range. Two reasons might contribute to the negative findings in volumetric measurement: ① Subtle hippocampal disease may show no hippocampal volume loss. Babb<sup>[2]</sup> had reported that hippocampus atrophy couldn't be detected until the neuron loss exceeds

50%. So MRI could not find hippocampal atrophy until significant volume loss present. ② Astrocytic gliosis could replace the volume when neuron loss or damage happened, in which cases the volume of HF remains unchanged. ③ Bilateral atrophy of hippocampus will yield normal DHF value<sup>[9]</sup>.

A major difficulty with <sup>1</sup>H-MRS *in vivo* is the presence of water and lipid, which interfere with proton metabolite signals. The temporal lobe is a challenging region to perform <sup>1</sup>H-MRS because it is close to petrous fat and ventricular CSF. Cuboids VOI were ap-

plied to include as much as temporal lobe structure and avoid nearby skull fat and CSF. The relative chemical shift of Cr and Cho peaks is only 0.2 PPM and the overlap of these peaks make the calculation of Cr and Cho very difficult. The concentration ratio of NAA/Cr+Cho is therefore widely used to evaluate the TLE patients<sup>[10,11]</sup>. The NAA/Cr+Cho value from control subject in our study was 0.74, which is consistent with that from Lu et al<sup>[11]</sup>. Our results showed that NAA/Cr+Cho ratio was significantly reduced in both ipsi- and contralateral hippocampus, with even lower value in seizure foci, suggesting that NAA/Cr+Cho was an ideal indicator to localize the seizure foci.

NAA is believed to be a sensitive marker of neuron, and Cho a membrane turnover chemical<sup>[12-14]</sup>. Decreased NAA/Cr+Cho and NAA/Cr ratios, combined with increased Cho/Cr value in ipsilateral hippocampus suggested that neuronal damage and reactive astrogliosis might both contribute to TLE, which were consistent with pathology findings of neuron loss and gliosis in the surgical resected epileptogenic foci. Epileptogenic foci could be lateralized in six patients using NAA/Cr+Cho threshold, indicating <sup>1</sup>H-MRS technique was more sensitive in finding HS than MRI. Neuron loss and/or gliosis in HS would show reduced NAA/Cr+Cho, and even mild HS could be detected by <sup>1</sup>H-MRS. Our result suggested that <sup>1</sup>H-MRS should be employed to assess the TLE patients who appear normal on the quantitative measurements in MRI.

Out of 6 cases without volumetric abnormality, 5 patients could be lateralized either by low or/and asymmetric NAA/Cr+Cho value detected on <sup>1</sup>H-MRS. One of the patients who had bilateral abnormal NAA/Cr+Cho could be lateralized by DHF data in MRI. Our findings emphasize the different and complementary nature of the information available from MRI and MRS. Combination of MRI and <sup>1</sup>H-MRS improve the sensitivity of detecting seizure focus.

In our study, reduced NAA/Cr+Cho ratio and increased Cho/Cr value were found in both the ipsi- and contralateral hippocampus of TLE patients. Contralateral hippocampus may be affected by repeated seizure activities, which resulted in neuron loss and/or glial hyperplasia in the affected area. It is reported that decreased contralateral NAA had poor surgical outcomes<sup>[15,16]</sup>. However, the predictive values of bilaterally

ally increased Cho/Cr ratio require further study.

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