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A study of the relationship between metabolism using ^{1}H-MRS and function using several neuropsychological tests in temporal lobe epilepsy

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Several investigators have reported on the relationship between metabolism, using magnetic resonance spectroscopy (MRS), and function, using neuropsychological tests in temporal lobe epilepsy (TLE) patients, but the opinions regarding the results remain in contention. The aim of this study is to examine the relationship between metabolism, using proton MRS (^{1}H-MRS), and function using several neuropsychological tests in the temporal lobes of TLE patients.

We studied 29 TLE patients at our hospital using ^{1}H-MRS and neuropsychological tests. We used a clinical 1.5 T MR unit. We conducted five neuropsychological tests to examine the function of the left or right temporal lobe.

There were significant correlations between the N-acetylaspartate/creatine + phosphocreatine (NAA/Cr) ratios and the scores of almost all of the neuropsychological tests for the temporal lobe function ipsilateral to the spike focus. However, in two Wechsler Memory Scale-Revised (WMS-R) subtests we found no significant correlation in the ipsilateral side.

These findings suggest that the NAA/Cr ratios, which reflect neural metabolism, are closely related to function in the temporal lobes of TLE patients. The disparity between the results in two subtests of WMS-R show that several tests may be necessary in order to assess temporal lobe function.

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Key words: brain function; brain metabolism; magnetic resonance spectroscopy; neuropsychological tests; N-acetylaspartate; temporal lobe epilepsy.

INTRODUCTION

Magnetic resonance spectroscopy (MRS) provides a noninvasive means of investigating various metabolites. Proton MRS (^{1}H-MRS) is able to show the presence of N-acetylaspartate (NAA), creatine + phosphocreatine (Cr), choline-containing compounds (Cho) and other various metabolites. Brain neurons contain NAA. The level of NAA indicates the metabolism of the neurons. This means that it is possible to examine the metabolism of neurons using ^{1}H-MRS[1,2]. Cr has the most stable concentration of the metabolites which are visible using ^{1}H-MRS. Therefore, the ratio of NAA to Cr (NAA/Cr) reflects the quantitative value of NAA[3]. Generally, the NAA/Cr ratio is adopted as an index of the NAA level.

Single-voxel ^{1}H-MRS is more sensitive in the temporal lobe than in other lobes which have spatial limitations restricting current techniques[4,5]. In temporal lobe epilepsy (TLE) several studies have already shown a close relationship between MRS abnormalities and the seizure focus[6–8].

There have been few reports on the relationship between metabolism and function of the brain, because *in vivo* it is very difficult to assess the metabolism of brain neurons, except by positron emission tomography (PET) studies[9–11] and MRS studies. In MRS studies, Gadian *et al.*[12] reported that in the temporal lobe, metabolism is closely related to function. These authors used the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and a subtest of the Wechsler Memory Scale (WMS) to examine the function.

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Martin *et al.*[13] reported that the results of neuropsychological tests using subtests of WMS and the Benton Facial Recognition Test are strongly associated with temporal lobe metabolism. However, Namer *et al.*[14] pointed out that although ^{1}H-MRS is weakly related to the function of the temporal lobe using WAIS-R and WMS-Revised (WMS-R), both ^{1}H-MRS and T_2 relaxation time values are important in order to analyse the function of the temporal lobe.

Opinions regarding the relationship between metabolism and function using MRS and neuropsychological tests remain in contention. One of the reasons for this is thought to be that the number of neuropsychological tests is too low at only two. It is necessary to conduct several neuropsychological tests that are sensitive to the functions of temporal lobes, because we do not have a well-established functional test of temporal lobes. The aim of this study is to examine the relationship between metabolism, using ^{1}H-MRS, and function, using several neuropsychological tests, in the temporal lobes of TLE patients.

MATERIALS AND METHODS

Subjects

We studied 24 unilateral (left. $n = 15$; right. $n = 9$; 12 men, 12 women) and five bilateral (two men, three women) TLE patients using ^{1}H-MRS and neuropsychological tests during the period of October 1997 to June 1999. The ages of the patients ranged from 18 to 66 years (mean = 38.9 years). Age at onset of epilepsy ranged from 5 to 54 years (mean = 22.4 years), and the duration of epilepsy varied from 2 to 58 years (mean = 16.3 years). We selected all of the patients from the outpatients attending the Neuropsychiatry Department of Gunma University Hospital. All of the patients were right-handed, and none had any abnormal neurological manifestations. We performed screening brain CT and MR studies on all patients to find gross neoplastic or vascular lesions, but such findings were not detected. Spike lateralization was produced in several scalp EEG recordings, in which focal spikes in the temporal lobe area were consistently found. We obtained informed consent from all of the patients.

^{1}H-MRS

We used a 1.5 T MR unit (Signa Horizon, General Electric, WI, USA). A series of coronal-fluid-attenuated inversion recovery (FLAIR) images of the hippocampi were obtained for localization. The settings were: repetition time (TR), 10 000 ms; echo time (TE), 150 ms; inversion time (TI), 2200 ms; flip angle, 180 degrees; 1 excitation; field of view (FOV), 220 mm × 220 mm; 256 × 192 matrix; slice thickness, 5 mm, gapless. The FLAIR images were obtained on a coronal plane. An approximately, $15 \times 15 \times 20$ mm^3 voxel of interest (VOI) was placed over the anterior portion of the hippocampus to encompass part of the bilateral hippocampal head and body. These placements avoided potential magnetic susceptibility artefacts from the base of the skull and the sphenoid sinus and contamination from fat in the base of the skull. Care was taken to ensure a standard placement in all of the subjects.

Water-suppressed single-voxel ^{1}H-MRS was used to apply point-resolved spectroscopy (PRESS). After the automated transmitter and receiver were adjusted, the signal over the VOI was shimmed to within a linewidth of 3–5 Hz. Optimal water suppression of 98–99% was achieved by pre-irradiation of the water resonance by applying three chemical-shift-selected pulses and spoiled gradients. A proton spectrum was then acquired (TR, 2000 ms; TE, 30 ms; 128 scans were averaged; bandwidth, 1600 Hz). The whole procedure was repeated on the contralateral hippocampus. The acquisition time for each VOI was 4 minutes 56 seconds.

The raw data were transferred to a SPARK 2 workstation (Sun Microsystems, CA, USA), and automatically post-processed using a spectroscopic analysis package (SA/GE, General Electric, WI, USA) according to the following steps: 1.0-Hz exponential apodization, zero-filling to 8 K, baseline correction, Fourier transformation, auto-phasing, and location of the Cr peak integrals by curve fitting. The NAA peak could be identified at 2.0 ppm, the Cr peak at 3.0 ppm. The integral value of each peak was dimensionless and represented the relative measurement of the amount of each metabolite. The semiquantitative result for each VOI was expressed as the ratio of NAA to Cr.

Neuropsychological tests

We conducted the following neuropsychological tests: the Rey Auditory Verbal Learning Test (AVLT), the Warrington Recognition Memory Test (WRT), the Benton Visual Retention Test (BVRT), four subtests (Logical Memory, Digit Span, Verbal Paired Associates, and Visual Reproduction) of the WMS-R, and two subtests (Information and Vocabulary) of the WAIS-R.

The AVLT is a measure of verbal memory and verbal memory retention using orally presented words. The WRT is a test of recognition memory for visually presented words and faces. The BVRT is a test of visual memory and visual memory retention using visually presented figures. The Logical Memory subtest of WMS-R is a recall test of two orally presented

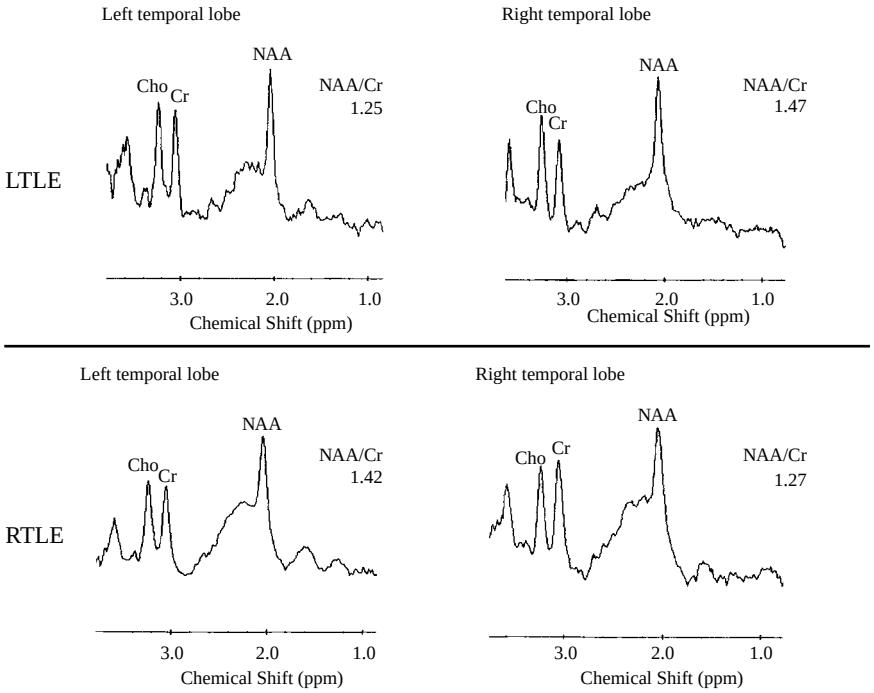

Fig. 1: Examples of ^{1}H-MR spectra from LTLE and RTLE patients. NAA/Cr is reduced in the ipsilateral side of spike focus. LTLE: a patient with left spike focus. RTLE: a patient with right spike focus. NAA: N-acetylaspartate. Cr: creatine + phosphocreatine, Cho: choline.

Table 1: The mean values of temporal NAA/Cr ratios and neuropsychological tests.

		NAA/Cr ratios		
		LTLE group ($n = 15$)	RTLE group ($n = 9$)	BTLE group ($n = 5$)
	Left NAA/Cr ratio	1.21 ± 0.11	1.32 ± 0.10	1.18 ± 0.20
	Right NAA/Cr ratio	1.41 ± 0.09	1.24 ± 0.12	1.30 ± 0.13
		Neuropsychological tests for left temporal lobes		
AVLT		46.87 ± 11.78	48.11 ± 8.55	35.60 ± 18.64
WRT	Word Recognition	45.60 ± 3.60	47.67 ± 1.50	38.20 ± 9.73
WMS-R	Logical Memory	13.10 ± 4.01	15.22 ± 2.37	9.50 ± 6.05
	Digit Span	8.53 ± 1.51	9.11 ± 2.32	9.20 ± 2.05
	Verbal Paired Associates	15.20 ± 4.80	16.22 ± 3.07	13.20 ± 6.98
WAIS-R	Information	12.60 ± 4.55	13.44 ± 6.73	9.00 ± 3.74
	Vocabulary	23.27 ± 11.67	31.78 ± 13.09	18.00 ± 10.65
		Neuropsychological tests for right temporal lobes		
WRT	Face Recognition	41.93 ± 3.51	38.67 ± 5.41	32.60 ± 9.53
BVRT	Number correct	7.73 ± 1.22	6.11 ± 1.90	5.40 ± 3.78
	Number of errors	3.07 ± 1.91	6.11 ± 3.98	8.80 ± 6.98
WMS-R	Visual Reproduction	30.30 ± 4.69	28.80 ± 6.88	29.20 ± 8.11

LTLE group: the patients with a left spike focus. RTLE group: the patients with a right spike focus. BTLE group: the patients with a bilateral spike focus.

stories. The Digit Span subtest of WMS-R is a recall test of digits. The Verbal Paired Associates subtests of WMS-R is a recall test of another word of the orally presented word pairs. The Visual Reproduction subtest of WMS-R is a test of visual memory and visual retention using visually presented complex figures. The Information subtest of WAIS-R assesses general knowledge. The Vocabulary subtest of WAIS-R requires the subjects to provide definitions of words.

For neuropsychological tests for the left temporal lobe function, we used the AVLT, the Word Recognition component of WRT, the Logical Memory I, the Verbal Paired Associates I and the Digit Span subtests of WMS-R, and the Information and Vocabulary

Table 2: The summary of Spearman's correlation analysis of the neuropsychological test scores vs. temporal NAA/Cr ratios.

		Left NAA/Cr ratios ($n = 29$) r Value	Right NAA/Cr ratios ($n = 29$) r Value
	Neuropsychological tests for left temporal lobes		
AVLT		0.623 [b]	0.188
WRT	Word Recognition	0.552 [b]	0.232
WMS-R	Logical Memory	0.575 [b]	0.115
	Digit Span	0.448 [a]	0.159
	Verbal Paired Associates	0.339	−0.014
WAIS-R	Information	0.566 [b]	0.416 [a]
	Vocabulary	0.642 [b]	0.260
	Neuropsychological tests for right temporal lobes		
WRT	Face Recognition	0.284	0.507 [b]
BVRT	Number correct	0.132	0.414 [a]
	Number of errors	−0.228	−0.424 [a]
WMS-R	Visual Reproduction	0.242	0.353

[a] $P < 0.05$, [b] $P < 0.01$.

subtests of WAIS-R. For neuropsychological tests for the right temporal lobe function, we used the BVRT (Form C, Administration A), the Face Recognition component of WRT, and the Visual Reproduction I subtest of WMS-R.

Statistical analysis

Correlation coefficients were tested using Spearman's product-moment correlation coefficient. $P < 0.05$ was considered to be significant.

RESULTS

Figure 1 shows spectra of both LTLE and RTLE patients extracted from bilateral temporal voxels. There are three clear peaks of Cho, Cr and NAA.

We classified the TLE patients into three groups. Fifteen patients had the spike focus in the left (the LTLE group), nine patients had the spike focus in the right (the RTLE group), and five patients had the spike foci in both temporal lobes (the BTLE group).

Table 1 shows the mean values for the NAA/Cr ratios and neuropsychological tests. In the left temporal lobes, the LTLE group had lower ratios than the RTLE group. In the right temporal lobes, the RTLE group had lower ratios than the LTLE group. In the TLE patients, the NAA/Cr ratios were reduced in the spike focus. In all of the neuropsychological tests for left temporal lobe function, the LTLE group had worse scores than the RTLE group. In all of the neuropsychological tests for right lobe function, the RTLE group had worse scores than the LTLE group.

We found no correlation between the NAA/Cr ratios and demographic information (patient's age, age at seizure onset, duration of illness and frequency of seizure).

Table 2 shows a summary of the correlations between the NAA/Cr ratios and the neuropsychological test scores for all of the patients. In neuropsychological tests for left temporal lobe function, there were significant correlations between the NAA/Cr ratios and the scores of all of the tests except the Verbal Paired Associates subtest of WMS-R. There was a significant correlation between the ratios in the right temporal lobe and the scores of the Information subtest of WAIS-R, and an even higher correlation in the left temporal lobe. In the neuropsychological tests for right temporal lobe function, there was no significant correlation between the ratios in the left temporal lobe and the scores of any of the tests. There were significant correlations between the ratios in the right temporal lobe and the scores of all of the neuropsychological tests except for the Visual Reproduction subtest of WMS-R. We found no correlations between the ratios in the left temporal lobe and the scores of the Verbal Paired Associates subtest of WMS-R, or between the ratios in the right temporal lobe and the scores of the Visual Reproduction subtest of WMS-R.

DISCUSSION

We used the AVLT, the WRT, the BVRT, and the WMS-R to test hippocampal function, because recent studies[15–19] have shown that these tests are related to hippocampal function. WAIS-R was originally an intelligence scale, but the Information and Vocabulary subtests are reported to reflect left temporal lobe functions[20]. WMS-R and WAIS-R are often used for TLE patients. However, a well-established functional test of

temporal lobes is not available at present. Therefore, in order to assess temporal lobe function more accurately, we believe it is important to conduct several tests that are thought to be sensitive to the functions of temporal lobes. We have selected five neuropsychological tests which we believe to be appropriate judging from previous reports[15–20].

Seizure focus using interictal data alone cannot always be precisely located, but in most patients, the seizure focus is detected using the interictal data. Therefore, we classified the subjects into three groups according to interictal spike focus in order to take into account the relationship between the seizure focus and metabolism, or between the seizure focus and function. In the TLE patients, we found that the NAA/Cr ratios were reduced in the spike focus. This result shows that MRS may reflect the abnormal metabolism resulting from the seizure. The scores of the neuropsychological tests for the temporal lobe function ipsilateral to the spike focus decreased.

There were significant correlations between the NAA/Cr ratios and the scores of almost all of the neuropsychological tests for temporal lobe function ipsilateral to the spike focus. There were no significant correlations between the ratios and the scores of any of the neuropsychological tests for the contralateral temporal lobe function except for the single subtest. These findings suggest that in the temporal lobes of TLE patients the NAA/Cr ratios, which reflect neural metabolism, are closely related to function. We can estimate the function of temporal lobes using ^{1}H-MRS in TLE patients. We may be able to easily examine temporal lobe dysfunction in TLE patients. It is important that we are able to locate the dysfunction easily in order to improve QOL in the patients.

Deficits on the Information and Vocabulary subtests of WAIS-R are generally seen in patients with lateral temporal pathology. Our WAIS-R results show that hippocampal MRS reflects not only the hippocampal function, but also lateral temporal function. The mechanism is unclear, but one of the causes might be that the voxels of hippocampal MRS include a considerable part of the parahippocampal region.

In two subtests of WMS-R, we found no significant correlation in the ipsilateral side. These results show that in order to assess the temporal lobe function correctly, it is important to conduct several tests that are sensitive to the functions of temporal lobes.

As techniques are developed, MRS will be able to detect more useful metabolites. It will become an important test of brain metabolism and will clarify the pathologic physiology of epilepsy.

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