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Investigation of patients with temporal lobe epilepsy using quantitative electroencephalography and magnetic resonance spectroscopy

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Abstract
Aim: Temporal lobe epilepsy (TLE) is the most common focal epilepsy in adulthood. Magnetic resonance spectroscopy (MRS) is an MRI technique used to measure regional variations in neurochemistry and display the concentrations of various brain metabolites in preset regions of interest in the brain. In this study, we aimed to evaluate the correlation of qEEG abnormalities and MRS findings in patients with temporal lobe epilepsy (TLE).
Material and Methods: Power spectrum analyses of each multi-channel EEG were performed in all patients with the concomitant MRS measures of Choline (Cho), total Creatine (Cr), N-acetyl aspartate (Naa) concentrations, and ratios of Cho/Cr, Naa/Cr, and Naa/Cho.
Results: Mean qEEG band powers of anterior alfa, anterior beta, central alfa, central beta, posterior alfa, and posterior beta in the right temporal area was significantly larger in patients whose Naa/Cho+Cr ratio was lower than 0.71 compared to patients whose Naa/Cho+Cr ratio was equal and larger than 0.71. In addition, correlation analyses between Naa/Cho+Cr, Naa/Cho+Cr, and Naa/Cho ratios and qEEG band power values showed low-medium correlations.
Discussion: A relationship detected between the biochemical changes of the epileptogenic focus due to neuronal dysfunction and the QEEG data may help prove the presence of the focal point.

Keywords
Temporal epilepsy; Quantitative electroencephalogram; MR spectroscopy

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Introduction

According to the World Health Organization (WHO), more than 50 million individuals are living with epilepsy, of whom nearly 80% live in middle- and low-income countries and do not get the proper treatment. Approximately 2.4 million individuals are diagnosed with epilepsy annually, and about %0.2 of all deaths in the world occur among this group of patients every year (available at: http://who.int).

Temporal lobe epilepsy (TLE) is the most common focal epilepsy in adulthood. In case of resistant seizures in TLE, further evaluation is required in terms of surgical intervention [1]. In mesial temporal lobe epilepsy (mTLE), seizures mostly originate in the hippocampal formation. The ipsilateral mesial temporal lobe is compatible with sclerosis in approximately 60% of patients with MTLE on magnetic resonance imaging (MRI) [2]. While 20-30% are normal, the rest have structural lesions (e.g, tumors or vascular malformations). Epileptogenic activity is usually not restricted to the hippocampus, but spreads to other brain regions as well, particularly to the temporal lobes, insula, and frontal lobes. [3]. Seizure symptoms are prominent in the evaluation of epileptic patients. However, the localizing value of seizure semiology is debated because currently seizure analysis is qualitative and based on visual inspection of seizure semiology [4].

Quantitative electroencephalogram (qEEG) is an attractive clinical tool, given its non-invasive nature, its ability to reflect real-time changes in local cortical activity, and a load of objective bioelectrical measurements that can be derived from it [5]. qEEG analyses have been used for evaluating and understanding neuro-psychiatric diseases nearly for the last fifty years. It is reported that fractional theta power was lower in patients with mesial temporal lobe epilepsy (MTLE) [6]. To improve spatial resolution, qEEG analysis has also been combined with medical imaging technology like magnetic resonance (MR).

MR spectroscopy (MRS) is a unique technique that allows the assessment of brain metabolism associated with cerebral compounds [7] and could detect certain metabolites such as between 0.5 and 1.0 mM concentrations in brain tissue [8]. Although it is known in theory that many compounds can be detected by MRS, in reality, compounds, where H protons are relatively high, can be detected. However, some of these components have clinical importance, such as N-acetyl aspartate (Naa), creatine (Cr), choline (Cho), lactate, lipids, and myoinositol [9].

MRS is a useful adjunct consistently demonstrating changing metabolites in the epileptogenic region, and the reduction of NAA is a typical finding in this area [8,10]. In addition, metabolite changes can also be identified outside the seizure focus in patients with TLE, reflecting a widespread disorder [11-12].

The most frequent findings were reported as decreased ratios of Naa to Cho and increased choline concentration in a study MR spectroscopic study of patients with MRI-negative extratemporal epilepsy. With these advances, qEEG may play a role in basic research and clinical studies on brain injury, neurological disorders, epilepsy, sleep studies and consciousness, and brain function [13]. With regard to this knowledge, in this study, we aimed to evaluate the correlation of qEEG abnormalities and MRS findings in patients with TLE.

Material and Methods

Forty-four patients (29 women and 15 men) aged between 13 and 70 years (mean age= 30.07±12.4) were included in this study, who were diagnosed as TLE according to the seizure semiology, examination findings, and qualitative EEG parameters. Patients with structural lesions, hippocampus atrophy, and/or sclerosis on conventional MRI and patients using any medication except antiepileptic drugs were excluded from the study.

EEG was recorded by the digital 32 channel apparatus Profile machine (Medelec Ltd U.K.) using the international 10/20 system and Ag/AgCl electrodes. EEG data were collected with linked mastoid reference. The power spectrum of each multi-channel EEG segment was computed on the basis of a Fast Fourier transformation of the data. For each channel, the powers in the delta, theta, alpha, and beta-band were calculated by summing components in bands from 0.5 to 3.5 Hz, 4 to 7.5 Hz, 8 to 13 Hz, and 13.5 to 20 Hz respectively. Amplified signals were bandpass filtered from 0.5 to 70 Hz. For each subject, 1 epoch of 10 s of multichannel EEG signals free of signs of impaired wakefulness, ocular movements, and other artifacts. qEEG analyses were performed according to the means of three areas: Fp1-Fp2-F3-F4-F7-F8-FZ (anterior), A1-A2-T3-T4-C3-C4-CZ (central), and P3-P4-T5-T6-O1-O1-PZ (posterior).

All subjects were scanned with a 1.5-T VISION MR system (GE Medical System, Milwaukee, WI, USA). Multi-slice MRS data (TR/TE = TR/TE: 3000/85), FOV; 14, Matrix; 352x352, Next; 1) were acquired from three 15-mm-thick slices aligned using T2 weighted fast spin-echo secants.

A single voxel was sequentially prescribed in hippocampal regions of each temporal lobe of each subject with an approximate dimension of 10 mmx10 mm. The volume of interest (VOI) placement was manual, and visual inspection ensured that these regions contained a predominantly hippocampal area of temporal lobe tissue. The very rostral slices of these volumes partially included basal ganglia structures, while the temporal pole and the anterior mesial temporal lobe structures were invariably excluded to ensure that the data quality remained acceptable. In both cases, the water signal was suppressed using 3 chemical-shift selective (CHESS) pulses, with the flip angle of the final pulse tailored to ensure slight under-suppression. Point-resolved spectroscopy (PRESS) localization was used to select the spectroscopy volume (TE/TR = 30/3000 ms). Finally, the short and medium timed TE of the VOI areas in both temporal areas was taken and data were analyzed using the program of the General Electric software spectral analyses. Monovoxel (TE, 35 ms) and multivoxel (TE, 144 ms) H-MR spectroscopy were performed on the temporal lobe tissue. Values of Cho, total Cr, Naa concentrations with the ratio of Cho/Cr, Naa/Cr, and Naa/Cho were used. The metabolic peak amplitudes were 3.23 for Cho, 3.03 for Cr, and 2.02 for Naa.

Statistical analyses

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. The univariate data for normal distribution were evaluated with the Shapiro-Wilk Francia test. In the diagnosis of MTLE and an epileptogenic

focus, the most sensitive MRS finding was reported as a decrease in Naa / Cho + Cr ratio, and in various studies, 0.70-0.71-0.72 and above rates were considered pathological margins, and 0.71 and below were used in our study [14]. Mann-Whitney U test was used with Monte Carlo simulation results in comparison of the grouped MRS findings (Naa / Cho + Cr) according to qEEG bands measurements. When comparing grouped MRS findings (Naa / Cho + Cr) by gender, Pearson Chi-Square and Fisher Exact tests were tested using Exact results. Partial Correlation test was used to examine the correlations between MRS findings and qEEG bands measurements in terms of gender and age. Quantitative variables were stated as median (minimum/maximum).

In the tables, categorical variables were shown as n (%). Variables were examined at a

95% confidence level, and p <0.05 was considered statistically significant.

Results

The mean age of the patients was 29.66 years, and the median value was found to be 24.50. The seizures started at the age of 17 on average, and the median value was 16.0. The annual average seizure frequency was 4.68 and the median value was 4.0. Patients' seizure characteristics were summarized in Table 1. Naa/Cho+Cr ratios were equal and higher than 0.71 in 19 (48.2%) and lower than 0.71 in 25 (56.8%) of the patients, and the difference was not statistically significant (p=0.366). The patients whose Naa/Cho+Cr ratio was lower than 0.71 were classified as Group 1 and the patients whose Naa/Cho+Cr ratio was equal and bigger than 0.71 were classified as Group 2 because the cut-off value for the Naa/Ch+Cr ratio is reported 0.70 in the hippocampal injury which is seen in patients with TLE. Mean qEEG band powers of anterior alfa (Ant A), anterior beta (Ant B), central alfa (Cent A), central beta (cent B), posterior alfa (post-A), and posterior beta (post B) on the right temporal area (right monovoxel) was significantly bigger in group 1

Table 1. Patients' seizure characteristics

	Age	Seizure Frequency	Seizure Age
Mean	29,68	4,68	17,43
Standard Deviation	12,00	3,40	6,33
Min	17,00	0,00	10,00
Percentile 25	20,75	2,00	14,00
Median	24,50	4,00	16,00
Percentile 75	34,00	7,00	19,00
Max	67,00	15,00	41,00

Table 2. Comparison of right monovoxel Naa/Cho+Cr ratios with qEEG

	MRS -Right monovoxel Naa/Cho+Cr ratios		P	MRS -Left monovoxel Naa/Cho+Cr ratios		P
	<0,71 (n=6)	≥0,71 (n=38)		<0,71 (n=9)	≥0,71 (n=35)	
	n (%)	n (%)		n (%)	n (%)	
GENDER						
Male	2 (33,3)	13 (34,2)	0,999[f]	5 (55,6)	10 (28,6)	0,235[f]
Female	4 (66,7)	25 (65,8)		4 (44,4)	25 (71,4)	
	Median (Min/Max)	Median (Min/Max)		Median (Min/Max)	Median (Min/Max)	
Age	34,50 (20/55)	23 (13/67)	0,096	28 (17/42)	24 (13/67)	0,660
qEEG bands						
Anterior alfa	12,90 (5,97/18,63)	3,94 (0,40/16,19)	<0,001	5,77 (0,73/12,97)	4,50 (0,40/18,63)	0,999
Anterior beta	5,16 (3,29/9,74)	2,37 (0,66/6,79)	<0,001	2,25 (1,05/3,97)	2,58 (0,66/9,74)	0,380
Central alfa	8,92 (5,88/18,48)	4,16 (0,51/15,78)	<0,001	6,07 (0,77/8,29)	4,81 (0,51/18,48)	0,780
Central beta	5,67 (3,03/10,36)	2,68 (0,80/7,24)	0,004	2,84 (0,86/4,33)	3,00 (0,80/10,36)	0,316
Posterior alfa	25,08 (15,11/77,63)	11,27 (0,66/63,15)	0,010	19,12 (1,26/32,05)	14,30 (0,66/77,63)	0,868
Posterior beta	7,69 (4,21/16,10)	3,25 (0,75/9,39)	<0,001	3,47 (0,90/5,79)	3,97 (0,75/16,10)	0,380

Table 3. Correlation analyses with significant results between MRS and qEEG band power values

MRS		qEEG bands											
		Anterior teta	Anterior delta	Anterior alfa	Anterior beta	Central delta	Central teta	Central alfa	Central beta	Posterior delta	Posterior teta	Posterior alfa	Posterior beta
monovoxel right Cho	r	-0,165	-0,376	-0,223	-0,285	-0,263	-0,092	-0,164	-0,195	-0,153	-0,065	-0,044	-0,083
	P	0,295	0,014	0,155	0,068	0,093	0,562	0,300	0,216	0,334	0,685	0,784	0,599
monovoxel right Cr	r	-0,005	-0,347	-0,271	-0,344	-0,199	0,058	-0,207	-0,303	-0,145	0,048	-0,113	-0,216
	P	0,973	0,024	0,082	0,026	0,207	0,716	0,188	0,051	0,360	0,764	0,475	0,169
monovoxel right Naa	r	-0,120	-0,385	-0,277	-0,475	-0,241	-0,081	-0,262	-0,413	-0,159	-0,047	-0,071	-0,277
	P	0,450	0,012	0,076	0,001	0,124	0,611	0,094	0,007	0,315	0,770	0,657	0,076
monovoxel right Naa/Cho + Cr	r	-0,247	-0,304	-0,223	-0,448	-0,239	-0,237	-0,260	-0,420	-0,173	-0,158	-0,023	-0,291
	P	0,115	0,051	0,156	0,003	0,128	0,130	0,096	0,006	0,274	0,317	0,884	0,062
monovoxel right Naa/Cho	r	-0,045	-0,362	-0,317	-0,384	-0,249	0,009	-0,300	-0,363	-0,190	0,023	-0,154	-0,313
	P	0,778	0,019	0,041	0,012	0,112	0,956	0,054	0,018	0,228	0,883	0,331	0,043
monovoxel left Cho	r	0,034	-0,221	-0,243	-0,306	-0,061	0,055	-0,171	-0,300	-0,039	0,053	-0,141	-0,216
	P	0,829	0,160	0,121	0,049	0,702	0,732	0,279	0,054	0,807	0,737	0,374	0,169
multivoxel right Cho/Cr	r	-0,212	-0,353	0,095	0,016	-0,303	-0,208	0,153	0,064	-0,251	-0,120	0,250	0,361
	P	0,178	0,022	0,551	0,921	0,051	0,187	0,335	0,686	0,109	0,450	0,111	0,019
multivoxel right Naa/Cho	r	0,178	0,395	0,106	0,122	0,280	0,120	0,125	0,067	0,211	0,060	-0,042	-0,173
	P	0,260	0,010	0,503	0,442	0,073	0,449	0,431	0,675	0,181	0,707	0,791	0,274

Partial Correlation Test, r: Correlation Coefficient, Age and Gender influence controlled

than group 2 but there was no significant difference in qEEG band powers of the left temporal area between groups and right multivoxel area (Table 2). Naa/Cho+Cr ratios and qEEG band power values showed a low-medium negative correlation between right monovoxel Naa/Cho+Cr anterior beta and central beta band powers. The other analyses between left monovoxel Naa/Cho+Cr, left multivoxel Naa/Cho+Cr, right multivoxel Naa/Cho+Cr between qEEG band power values were not statistically significant. Correlation analyses between Cho/Cr ratios and qEEG band power values showed a low-medium negative correlation between right multivoxel Cho/Cr ratio and anterior delta band power value (r=-0.353 p=0.022) and low-medium positive correlation between right multivoxel Cho/Cr ratio and posterior alfa and posterior beta band powers (r=0.361 p=0.019). The other analyses between left monovoxel Cho/Cr, left multivoxel Cho/Cr, right monovoxel Cho/Cr, and qEEG band power values were not statistically significant (p>0.05). Correlation analyses between Naa/Cho ratios and qEEG band power values showed a low-medium negative correlation between right monovoxel Naa/Cho ratio and anterior beta band power value. In addition, low-medium positive correlation was found between the right multivoxel Naa/Cho ratio and anterior delta band power values (Table 2). Other analyses between left monovoxel Naa/Cho and left multivoxel Naa/Cho with qEEG band power values were not statistically significant ((p>0.05). Naa/Cr ratios and qEEG band power values were not statistically significant. Correlations were summarized in Table 3. There was not a statistically significant correlation between MRS findings with clinical (seizure frequency) and EEG (existence of left temporal, and bilateral temporal EEG abnormality) properties (p>0.05).

Discussion

Quantitative EEG plays a significant role in investigating brain activity. In a study evaluating the qEEG power in sclerotic and non-sclerotic MTLE patients, the authors reported that total and delta band power was lower in sclerotic patients, while there was no difference in the gamma and beta powers [15]. Most of the studies had focused on the correlation of qEEG findings with conventional MRI; however, this study mainly focuses on the association of qEEG findings with MRS.

Proton magnetic resonance spectroscopy (1H-MRS) has played an important role in detecting metabolic alterations in patients with TLE, although its popularity lags behind PET and single-photon emission computed tomography (SPECT) in the presurgical evaluation of MRI-negative TLE. N-Acetyl aspartate (NAA) is synthesized only in neuronal mitochondria, and a relatively higher concentration of creatine is found in astrocytes. The reduction of NAA signal is believed to be associated with neuronal loss or dysfunction, whereas an increase in creatine (Cr) signal suggests gliosis. Hence studies tend to use the NAA/Cr ratio as a marker of the neuronal function of the neuronal-glial unit. Perhaps more importantly, the NAA/Cr alterations picked up by MRS imaging have been shown to reflect neuronal and glial dysfunction rather than neuronal cell loss [16]. This makes the marker relatively independent of tissue atrophy. Reduced levels of NAA/Cr or NAA/Cr+Cho in patients with TLE have been found beyond the ipsilateral hippocampus, involving regions such as the thalami, insula, frontal lobes, parietal lobes, and contralateral hippocampus [17,18].

Atrophic hippocampus typically does have lower Naa/Cr and is generally regarded as clearly injured, the ratio is not specifically determined by volumetric loss, and likely more reflects mitochondrial function [19]. In this study, we could not find any relation between Naa/Cr ratio and qEEG band power. This result would be explained by concomitant but different pathogenetic factors causing both MRS pathologies and qEEG abnormalities. It is known that, with the exception of the thalamus and Wernicke area, there are no significant differences in metabolite concentrations between hemispheres in the healthy brain [20]. However, it is well known NAA/Cr, NAA/Cho, and NAA/(Cho+Cr) are decreased in both temporal and extratemporal epilepsies [21]. In a study performed by Bernasconi et al, no significant difference was found in the amount of delta activity in the temporal lobe between the controls and patients, and no correlation was found between the delta activity and the neuroimaging measures [22]. In our study, we found some significant differences in qEEG measures according to Naa/Cho+Cr ratios. Our results suggest that means of high-frequency powers in qEEG (anterior alfa and beta, central alfa and beta, posterior alfa and beta) are significantly higher in patients whose Naa/Cho+Cr ratio was lower than 0.71. Naa/Cho+Cr ratio reflects a neuronal dysfunction in the interested area of MRS analysis (right temporal area - monovoxel), however, there was not any significant difference in the right multivoxel measures. These results can be explained by the technical properties of MRS, in which long TE time MRS measures are better in fluid attenuation and lessening artifacts due to fat contamination [22-23].

Correlation analyses between ratios of Naa/Cho+Cr, Cho/Cr ratio, and Naa/Cr with qEEG band powers were performed in this study. Although the correlation analyses of left and right hemispheres were not always compatible, we think these results would be explained by localized back-ground rhythm properties and neuronal dysfunction due to epileptic activity [24]. Results of evaluations focusing on correlation of MRS values with some qEEG band powers were statistically significant in our study, but we think it is not convenient to attribute some pathogenetic associations with these electrophysiological and imaging findings without any clinical consistency.

In this study, correlation analyses between seizure frequency and temporal abnormalities with MRS findings were also performed. A positive correlation between MRS findings with lateralized epileptogenic focus and seizure frequency had been reported before [25], however we did not get similar results. This result would be explained by the differences in the criteria for patient selection. Because seizure frequency was low in most of the patients in our study, the patients with structural lesions, hippocampus atrophy, and/or sclerosis on conventional MRI were not included.

Conclusion

Lateralization of the epileptic focus with localization by the help of seizure semiology and routine EEG and performing more limited qEEG analyses instead of performing all qEEG band powers in anterior, central, and posterior parts of the hemispheres would be more compatible for the present study.

Despite limitations, such as lack of control group and a detailed clinical questionnaire that would be helpful to lateralize epileptic focus, our study's results suggest that there is no strong but low-medium correlation between qEEG and MRS findings of patients with TLE.

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Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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