THE RELATION BETWEEN CLINICAL, EPILEPTIFORM DISCHARGES, AND NEUROMETABOLIC DYSFUNCTION IN TEMPORAL LOBE EPILEPSY

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ABSTRACT

Background: Temporal lobe epilepsy (TLE) is the most frequent cause of focal and refractory seizures. Magnetic Resonance Spectroscopy (MRS) is a potentially useful tool in the investigation of brain metabolites in TLE. **Objective:** to clarify the role of MRS in the TLE epilepsy and to evaluate the relationship between the results of MRS, Electroencephalography (EEG), and the clinical data of TLE patients with negative Magnetic Resonance imaging (MRI). **Patients & Methods:** Thirty patients with TLE and negative MRI were investigated by EEG, MRS and neuropsychological tests that assessed memory function of temporal lobe. By using temporal metabolite identified on MRS, we could detect metabolic disturbance that occur in TLE and tried to lateralize epileptic focus. We correlated MRS results with, EEG results, and the patient's scores on memory function tests. Twenty age-matched volunteers were used as control subjects. **Result(s):** Ipsilateral temporal N-acetyl-aspartate (NAA)/ Creatine+Choline (Cr+Cho) and NAA/Cr ratios of the patients were significantly reduced compared with the mean ratios of contralateral hippocampus ($p < 0.001$) and control subjects ($p < 0.001$). EEG could detect epileptic focus in 17 (56.7%) patients, while MRS could detect epileptic focus in 27 (90%) patients and could lateralize about 76.9% of patients with bitemporal interictal epileptiform discharges (IEDs). Significant negative correlation between ipsilateral temporal NAA/Cr+Cho, NAA/Cr ratios and ipsilateral IEDs ratio ($p < 0.05$). Left temporal NAA/Cr ratio correlated significantly with patient's scores on Rey Auditory Verbal Learning Test (RAVLT) ($p< 0.05$) and right temporal NAA/Cr ratio correlated significantly with patient's scores on Rey Complex Figure Test (RCFT) ($p < 0.05$). **Conclusion(s):** These findings suggested that the temporal metabolite ratios identified on MRS could lateralize epileptic focus in TLE patients and they are closely related to the temporal IEDs and the cognitive function of temporal lobe.

Key Words: temporal lobe epilepsy, Magnetic resonance spectroscopy, EEG, memory.

INTRODUCTION

Temporal lobe epilepsy (TLE) is one of the most common forms of partial or focal epilepsy which is observed in about 40% of patients with epilepsy. TLE is a subtype of epilepsy in which individuals present with seizure semiology and electroencephalographic characteristics that point to an ictal onset in mesial temporal structures [(1)]

About 30% of patients with TLE are resistant to antiepileptic drugs and may need surgical treatment [(2)]**.** Correct lateralization of the affected hemisphere with precise localization of the epileptic foci is a prerequisite for good surgical outcome, but it remains a challenge especially for non lesional epilepsy and bilateral TLE. Up to 30% of patients with TLE have no detectable structural lesions on modern MRI [(3)]**.** Non invasive focus localization by intensive video EEG monitoring in mesiotemporal structures does not always lead to clear focus [(4)]**.**

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) has been shown to be a useful tool in investigation in vivo and non invasively key molecules of brain metabolism relevant to patho-physiology and neuropathology of temporal structures involved in TLE [(5)]**.** N-acetyl aspartate (NAA) is the meta-bolite commonly evaluated; it resides primarily in healthy neurons and precursor cells and can be regarded as a neuronal marker. Creatine (Cr) is a ubiquitous compound found in glial cells and is related to the energy metabolism. Choline (Cho) is bound to cell membranes, myelin, and complex brain lipids [(6)]**.**

Most TLE patients have progress-sive memory deficits and in these patients, careful memory evaluation is needed. MRS is a functional imaging technique which gives information not only about epilepsy lateralization but also about brain function [(7)]**.**

In the present study, we aimed to clarify the role of MRS in TLE and to evaluate the relationship between the results of MRS, EEG results, and the clinical data of TLE patients especially in those patients with negative MRI.

PATIENTS AND METHODS

This study was carried out in Neurology Department and Neurology Outpatient clinic, Zagazig University Hospitals during the period from September 2012 to November 2014. This

study was conducted on thirty right handed TLE patients (16 males and 14 females). Their age ranged from 19 to 45 years with a mean age of 31.7 ± 7.4 years. Diagnosis of TLE was based on guidelines proposed by International League against Epilepsy (ILAE) [8] (1989), history of seizure description, results of prolonged video monitoring EEG, and MRI. Inclusion criteria were designed for the patients as follow; age ≥ 18 years, unprovoked seizures of tempo-ral lobe origin as shown by seizure description and results of interictal EEG, educated patients and temporal lobe epileptic patients with normal brain MRI. These patients were compared with 20 healthy control subjects (10 males and 10 females), their age ranged from 20 to 44years, with a mean age 32±6.8. The control subjects matched for mean age, gender, and educational state with the patient's written informed consent were obtained from the patients and control subjects.

All patients and control subjects were subjected to; Full history taking and complete general and neurological examination.

Video EEG monitoring

All patients were submitted to prolonged video EEG monitoring (within 24 hours) using XM3- 19 W LCD monitor, XEROX. Electrodes were placed according to 10- 20 system. The EEG tracing were analyzed carefully as regarding the background activity, and presence of interictal and ictal epilep-tiform discharges (IEDs). IEDs were manually counted on the basis of morphological criteria (i.e transients clearly distinguishable from background activity, with characteristic morphology and duration of 70 – 200 ms [9]. The lateralization ratio of IEDs was calcu-lated by expressing the number of IEDs counted on the either side, as a percentage of the total number of IEDs recorded on both sides. Unilateral IEDs required a minimum of 80% of laterali-zation (80% or more of IEDs were recorded over one side). If this ratio was less than 80%, the patient was considered to have bitemporal IEDs [10].

Magnetic Resonance imaging (MRI)

All patients and control subjects were examined by the MRI of the brain at MR units of Radiology Department of faculty of medicine, Zagazig University Hospitals using 1.5 Tesla Philips Achiva with a standard head coil and the following sequences : sagittal , axial, and coronal T_1 – weighted images (500-600 \12) time of repetition TR / time of echo TE at 2 mm slice thickness .T_2 – weighted images in coronal and axial plan with (2800 TR / 80 TE), and T_2W FLAIR perpendicular to the long axis of the hippocampus.

Magnetic Resonance spectroscopy (MRS)

Single voxel spectroscopy was performed within 2-3 weeks either before or after video EEG monitoring, assuming that total metabolic measure-ments remained constant during such a short period [11]. To obtain optimal signal demarcation of hippocampal structure from amygdale and especially from the ventricular system and to exclude cerebrospinal fluid (CSF) contamination, sagittal, transversal ,coronal T_2 weighted images in three orthogonal planes were used as localizer : (a) T_2w sagittal : distance factor 20%, FOV ,255x 204 mm ;TR , 4,930ms ; TE, 98ms ,slice thickness , 3mm (b) T_2w transversal (angulated parallel to the axis of the hippocampus): FOV 280 mm ; slice thickness , 3mm (c) T_2w coronal : FOV 260mm , slice thickness 3 mm ; total time was 10 Minutes . Water supper-ssion was achieved by three chemical shift selective (CHESS) pulses before the point Resolved Spectroscopy (PRESS); repetition time (TR) 3,000ms; echo time (TE) 30ms. The voxel comprised the head and anterior body portions of the hippocampus. The voxel size was reduced to a minimum volume of 2 cc arising from an edge length of 20 mm in the sagittal axis and 10 mm in coronal and horizontal axis. Metabolites signal peaks were centered as following ; NAA at 2 ppm , Cr at 3.31ppm , Cho at 3.2 ppm , Lac at 1.3 – 1.4 ppm , Glx at 2.45 ppm and MI at 3.6 ppm . The NAA/ Cr, or NAA/ Cr + Cho ratios were being calculated for each voxel.

The NAA, Cho and Cr concentra-tions and NAA/ Cr, NAA/ Cr+Cho ratios compared between left and right hippocampi in each patient. The patient's values were compared with mean control's values.

Lateralization of the seizures focus or ipsilateral side by MRS data was as follows:

NAA/ Cr and NAA/ Cr+Cho ratios which were ≤ 2 SD of the mean of the control subjects ,were considered abnormal or ipsilateral side .This could be either unilateral or bilateral , if unilateral the side of the abnormal values was considered to be the abnormal side

or ipsilateral side , if both sides were abnormal with Asymmetry index (AI); the percentage of metabolic ratio reduction difference between ipsilateral and contralateral sides was ≥ 12% , the sides of the lower values was considered to be the ipsilateral or abnormal side, whereas if AI ≤ 12% , no lateralization was defined [12]. Asymmetry indices (AI) for NAA/ Cr or NAA/ Cr+Cho ratios between ipsilateral and the contralateral side in the patients were calculated as follows according to Vermathen et al [13].

$$\frac{M\ contralateral - M\ ipsilateral}{\left(M\ contralateral + Mipsilateral/2\right)} x100$$

According to MRS data on the lateralization of the seizures focus, we divided the patients into right (R) and left (L) TLE patients.

Neuropsychological Assessment

We conducted the following neuropsychological tests; Rey Auditory Verbal Learning Test (RAVLT) to assess verbal memory and left temporal lobe function. Rey Complex Figure Test (RCFT) to assess visual memory and right temporal lobe function [14].

Statistical Analysis

All data were collected, tabulated and statistically analyzed using SPSS 15.0 for windows (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for windows (MedCalc Software bvba). Independent Student t-test, Mann-Whitney U (MW) test, Chi-square (χ^2) test, Pearson's correlation coefficient (‡) and Spearman's rank correlation coefficient (§) were used as tests of significance. Significance was considered when p value was less than 0.05.

RESULTS

There were highly significant differences between the mean ipsilateral hippocampal NAA/Cr and NAA/Cr +Cho ratios of our patients and the mean ratios of control subjects (p1<0.001), (p1<0.001). The mean ipsilateral hippocampal NAA/Cr and NAA/ Cr+ Cho ratios of our patients were signify-cantly reduced compared with the mean contralateral hippocampal ratios (p3<0.001), (p3<0.001). In our patients the mean NAA/Cr and NAA/Cr+Cho ratios on the contralateral hippocampus were signifi-cantly lower than the mean ratios of the control subjects (p2< 0.001), (p2<0.001) (Table 1).

To compare the abilities of EEG and MRS to lateralize epileptic focus in the patients with TLE, we found that MRS results could detect epileptic focus in 27 (90%) patients, 12(40%) patients had right epileptic focus and 15(50%) patients had left epileptic focus, while MRS results failed to detect epileptic focus in 3(10%) patients. EEG results could detect epileptic focus in 17 (56.7%) patients, 7(23.4%) patients had right epileptic focus versus 10 (33.3%) patients had left epileptic focus. The remaining 13 (43.3%) patients could not be lateralized by EEG results. MRS had a significant role in the lateralization of epileptic focus in comparison with EEG results (p<0.05) (Table 2).

To evaluate the agreement between the lateralization of epileptic focus by EEG and MRS results, we found that MRS indicated concordant lateralization to EEG results in 100% of patients with unitemporal IEDs. MRS detected epileptic focus in 10 patients of 13 patients with bitemporal IEDs, while it could not detect epileptic focus in 3 patients with bitemporal IEDs (Table 3).

There were significant negative correlation between ipsilateral temporal NAA/Cr , NAA/Cr+Cho ratios and total IEDs (p =0.01), (p =0.01), ipsilateral IEDs ratio (p=0.04), (p=0.03) (Table 4).

On RAVLT (immediate, delay, post), performance of the left TLE patients were significantly lower than that of the control subjects (p< 0.001) and right TLE patients (p<0.001). On RCFT (copy, immediate, delay) there were significant differences between the groups. The right TLE performed worse than the control subjects (p< 0.001) and left TLE patients (p< 0.001) (table 5).

Regarding the correlation between the temporal lobe metabolic ratios and temporal lobe functions, we found that in the right TLE patients, right temporal NAA/Cr ratio did not correlated significantly with cognitive function test of the left temporal lobe including, RAVLT(immediate, delay, post) (p >0.05). There were a highly significant correlation between right temporal NAA/Cr ratio and cognitive function test of right temporal lobe including RCFT (copy, immediate, delay) (p>0.001). In the left TLE patients, right temporal NAA/Cr ratio did not correlated with

RAVLT (immediate, delay, post) (p>0.05) and it correlated significantly with RCFT (copy, immediate, delay) (p<0.05). Regarding the left temporal NAA/Cr ratio of right TLE patients, we found that this ratio correlated significantly with RAVLT (immediate, delay, post) (p< 0.05), however it did not correlated significantly with RCFT (copy, immediate, delay) (p>0.05). In the left TLE patients, there were highly a significant positive correlation between left temporal NAA/Cr ratio and RAVLT (immediate, delay, post) (p<0.001), but this ratio did not correlated significantly with RCFT (copy, immediate, delay) (p> 0.05) (table6).

Table (1): Temporal NAA/Cr and NAA/Cr+Cho ratios of TLE patients and control subjects.

Metabolic ratios	Patients (N=30)		Controls (N=20)	Test (p1)	Test (p2)	Test (p3)
	Ipsilateral	Contralateral				
NAA/Cr				**MW**	**MW**	**WSR**
▪ **Mean ± SD**	1.26±0.23	1.73±0.34	2.26±0.24	-5.949 (<0.001)**	-5.096 (<0.001)**	-4.783 (<0.001)**
▪ **Median**	1.32	1.87	2.35			
NAA/Cho+Cr				**MW**	**MW**	**WSR**
▪ **Mean± SD**	0.46±0.07	0.78±0.16	1.00±0.05	-6.015 (<0.001)**	-5.580 (<0.001)**	-4.784 (<0.001)**
▪ **Median**	0.46	0.82	1.00			

p1 denote p value of test of significance between ipsilateral & controls; p2 denote p value of test of significance between contralateral & controls; p3 denote p value of test of significance between ipsilateral & contralater.

Table (2): Lateralization of epileptic focus in TLE patients by EEG and MRS results.

	EEG results		MRS results		χ^2	p
	No	%	No	%		
Unilateral TLE	(17)	(56.7 %)	(27)	(90 %)	8.566	0.013*
Right temporal	7	23.4 %	12	40 %		
Left temporal	10	33.3 %	15	50 %		
Bilateral TLE	(13)	(43.3 %)	(3)	(10 %)		

Table (3): Agreement between lateralization of epileptic focus by EEG and MRS results.

EEG results	MRS results				Total	
	Unilateral TLE		Bilateral TLE			
Unitemporal (n=17)	17	(56.7 %)	0	(0 %)	17	(56.7 %)
Bitemporal (n= 13)	10	(33.3 %)	3	(10 %)	13	(43.3 %)
Total	27	(90 %)	3	(10 %)	30	(100 %)

Table (4): Correlation between ipsilateral temporal lobe metabolic ratios and interictal epiletiform discharges.

	Ipsilateral NAA/Cr		Ipsilateral NAA/Cr +Cho	
	r	**p**	**r**	**p**
Total IEDs	- 0.861§	0.01 *	- 0.871§	0.01 *
Ipsilateral IEDs ratio	- 0.790§	0.04 *	- 0.830§	0.03 *

Table (5): A comparison between TLE patients and control subjects regarding memory tests.

Memory tests	Patients		Controls	Test (p1)	Test (p2)	Test (p3)
	R TLE	L TLE				
L temporal lobe function				**MW**	**MW**	**MW**
RAVLT immediate	38.5 ±6.4	24.7 ± 4.1	55.5± 3.3	-5.67 <0.001	-6.42 <0.001	-4.32 <0.001
RAVLT delay	8 ± 1.9	4.8 ± 0.8	11.7± 1.3	- 5.33 <0.001	- 6.10 <0.001	- 4.53 <0.001
RAVLT post	7.8±1.4	5 ± 0.7	11.8± 0.7	- 4.76 <0.001	- 5.87 <0.001	- 4.26 <0.001
R temporal lobe function				**MW**	**MW**	**MW**
RCFT copy	25.1± 3.7	27.7±3.8	32± 1.5	-4.34 0.03	-4.11 0.05	-1.13 0.09
RCFT immediate	12.1 ± 2	17.2 ± 2.5	21± 1	- 5.66 <0.001	- 4.22 0.001	- 4.1 <0.001
RCFT copy	8.7 ± 2.4	12.9 ±3.5	16± 1.3	- 5.87 <0.001	- 3.87 0.05	- 5.12 <0.001

p1 denote p value of test of significance between R TLE patients & controls; p2 denote p value of test of significance between L TLE patients & controls; p3 denote p value of test of significance between R & L TLE patients

Table (6): Correlation between temporal NAA/Cr ratio and memory tests scores of TLE patients.

	Right NAA/Cr				Left NAA/Cr			
	R TLE		L TLE		R TLE		L TLE	
Left temporal lobe functions	r	(p)	r	(p)	r	(p)	r	(p)
RAVLT immediate	+0.26	(0.37)	+0.35	(0.2)	+0.74	(0.01)	+0.88	(<0.001)
RAVLT delay	+0.20	(0.46)	+0.43	(0.1)	+0.62	(0.03)	+0.77	(0.001)
RAVLT post	+0.14	(0.61)	+0.04	(0.8)	+0.68	(0.02)	+0.79	(<0.001)
Right temporal lobe functions								
RCFT copy	+0.87	(<0.001)	+ 0.8	(0.002)	+0.13	(0.68)	+0.23	(0.07)
RCFT immediate	+0.88	(<0.001)	+0.87	(<0.001)	+0.32	(0.07)	+0.28	(0.37)
RCFT delay	+0.84	(0.001)	+ 0.74	(0.003)	+0.34	(0.06)	+0.26	(0.54)

DISCUSSION

Empirical evidence indicates that 1H-MRS can offer additional information for clinical diagnosis and evaluation of therapeutic strategies in patients with TLE [(15)]. In this work, we could detect the metabolic disturbances that occur in the patients with TLE, that are not associated with any structural changes in MRI as we found significant reduction of temporal NAA/Cr and NAA/Cr +Cho ratios in the patients compared to these ratios of the control subjects. In addition, our patients showed marked reduction of these ratios in the ipsilateral hippocampus in comparison to the contralateral hippocampus. These findings are consistent with the results of **Aristides et al** [(12)]; **Ahmed** [(16)]; **Qi et al** [(17)]; **Shaker** [(18)]. **; and Abd El hameed.**[(19)] who reported that in patients with TLE , the mean NAA/Cr and NAA/Cr + Cho ratios decreased significantly in

the ipsilateral hippocampus in comparison to that in control subjects and contralateral hippocampus. **Suhy et al.** [20] study showed that NAA was reduced in the epileptogenic hippocampus frequently, even when MRI is normal, suggesting that NAA can help to identify the seizure focus. To highlight the possible causes of NAA reduction in TLE patients with normal MRI in detail, first report attributed NAA reduction to irreversible neuronal tissue degeneration and cell loss [21]. In later studies, alterations of NAA were also associated with neuronal dysfunction, reflecting a reversible dynamic state not principally characterized by tissue damage [22, 23]. In addition **Hammen et al.** [11] reported that NAA reduction might be the result of oxidative stress in neurons exhibiting increased electrical irritability. Cr and Cho concentrations are higher in glial cell than in neurons. Therefore increased Cr signals may reflect gliosis which is a common finding in TLE [23]. Finally **Zhang et al.**[4] in their published data found that MRS could detect the biochemical abnormalities before the appearance of morphologic changes and may allow detection of subtle patholo-gies in patients with normal MRI**.**

Regarding the results of EEG and MRS, we found that EEG could lateralize about 56.7%of our TLE patients. By using NAA/Cr and NAA/ Cr+Cho and A.I of these ratios, we could lateralize epileptic focus in 90% of our patients. MRS indicated concordant hemispheric lateralization to EEG findings in 100% of our patients with unitemporal IEDs and could lateralize about 76.9% of patients with bitemporal IEDs. These results were supported by **Qi et al.** [17] who found that EEG could lateralize 50% of their TLE patients, while MRS could lateralize about 87% of those patients. **Someya et al.**[24] demonstrated that EEG could not lateralize about 52% of their TLE patients,while MRS could lateralize 89% of those patients. **Riederer et al.**[25] reported that correct spectroscopic focus lateralization was carried out in 85% of TLE patients. **Salmenpera et al.** [26] found that MRS lateralized seizures focus in up to 88% of TLE patients. **Aydin et al.** [27] reported that 1H-MRS offer a lot of qualitative and quantitative data which can help to localize the epileptic lesions and provide an insight into biophysical and biochemical processes related to epileptic seizures. They concluded that the sensitivity of MRS for lateralization epileptic focus was 96%, with specificity was 55%. Finally according to our results and the previous studies we suggested that MRS has a much higher accuracy of focus lateralization in TLE patients with negative MRI than EEG.

In localization – related epilepsy, the hallmark of an area of abnormal increased excitability in the cortex is the interictal spike discharge seen in EEG [28].To evaluate whether IEDs correlated with temporal metabolite ratios in patients with TLE, our results revealed a significant negative correlation between ipsilateral temporal NAA/Cr+ Cho, NAA/Cr ratios and ipsilateral IEDs ratio that were captured by prolonged video EEG monitoring. These results were matching to the results of **Garcia et al.** [28]**; Shih et al.**[22] and **Azab et al.** [29]. **Serles et al.** [30] suggested that higher interictal spike frequencies on surface EEG were closely related to the regions of pronounced neuronal metabolic damage or dysfunction. In our study, we found also a significant negative correlation between ipsilateral NAA/ Cr+Cho, NAA/Cr ratio and total IEDs. It is most likely that the contralateral epileptogenicity may have been resulted from the process of secondary epilepto-genesis due to massive repetitive electrical discharges from ipsilateral side which result in increased total IEDs [31].

Temporal lobe epilepsy is frequently associated with impairment of memory function [32]. In our study, we are able to clarify that Performance of our patients was worse than the controls in all neuropsychological tests. Our findings were in agreement with prior results of **Hermann et al**. [33] **and Marques et al.** [34] who found that patients with TLE performed in impaired fashion across variety of cognitive domains. As regard the comparison between left and right TLE patients on cognitive domain measures, we found that left TLE patients obtained significant lower scores on AVRLT than right TLE patients. The left TLE patients performed better than right TLE patients in RCFT (immediate, delay). These results are in agreement with **Samir.**[35] **and Wisniewski et al.** [36] who found that Left temporal epileptic

focus influences verbal memory while focal right TLE has a greater effect on visual memory

In our work, we found that in both left and right TLE patients there were significant correlation between the left temporal NAA/Cr ratio and the patient's scores of the neuropsychological tests for the left temporal lobe functions that included RAVLT. On the other hand the left temporal NAA/Cr ratio did not correlate with the patient's scores of any of neuropsychological test for the right temporal lobe functions included RCFT. Our results were in agreement with some previous studies of **Hanoglu et al. [37] ; and Mantoan et al [10] . Sawire et al. [38]** in their study reported that the left hippocampal NAA is more sensitive to episodic verbal memory or the left temporal lobe function than the volume of hippocampus. In both groups, we reported significant correlation between the right temporal NAA/Cr ratio and the patients' scores of RCFT but this ratio did not correlate with the patient's scores of RAVLT. These results went side by side to the results of **Kikuchi et al [39] and Mantoan et al [10].** These findings suggested that in each temporal lobe of TLE patients, the NAA/Cr ratio which reflects neuronal metabolism, are closely related to function of that temporal lobe and we can estimate the function of temporal lobes by using 1H-MRS **[40].** The relation between patient's metabolic ratios and their scores on several memory tests could be explained by neuronal dysfunction caused by epileptic activity, which results in reduced performance on memory and general cognitive tests. It is possible that subclinical seizures activity during testing could affect their performance on these tests [41].

CONCLUSION

MRS provides important information concerning the neuronal metabolic changes for accurate lateralizing of the epileptogenic focus in TLE patients, especially in the patients without pathologic findings in MRI and the patients who had bitemporal epileptiform discharges. MRS proved to be a sensitive procedure to evaluate the severity of TLE as displayed by the degree of interictal activity on EEG. Metabolic abnormalities in the hippocampus identified on MRS are associated with impaired memory performance.

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