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ORIGINAL STUDY

Lateralizing Ability of Magnetic Resonance Spectroscopy and Diffusion Tensor Imaging in Temporal Lobe Epilepsy

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Abstract

Background: **Temporal lobe epilepsy (TLE) is the most common type of intractable and partial epilepsies. The only standard treatment for seizure-free status with manifest TLE is surgical, which includes amygdalohippocampectomy. The majority of temporal lobe seizures originates in the mesial temporal structures, primarily in the hippocampus, parahippocampal gyrus, and amygdala.**

Objectives: **To compare the lateralizing ability of magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) in patients with TLE.**

Patients and methods: **The study recruited 50 participants who were assigned into two groups: the first group included 25 epileptic cases and the second group included 25 normal controls. Age showed a mean ± SD of 24.22 ± 9.7 years. All participants were subjected to the following, clinical assessment, electroencephalography, and radiological assessment including MRI epilepsy protocol, MRS, and DTI. Data were collected, revised, then extracted, and coded in Excel files.**

Results: **MRS has demonstrated consistent metabolic abnormalities in partial seizures. Semiology showed the highest and the most perfect diagnostic ability indices for epilepsy (100%), followed by MRS (accuracy = 92%), and DTI difference more than or equal to 0.014 (accuracy = 86%).**

Conclusion: **Semiology showed the highest and the most perfect diagnostic ability indices for epilepsy (100%).
MRS is a highly sensitive tool to predict the TLE (accuracy = 92%).
DTI difference more than or equal to 0.014 (accuracy = 86%), so it has high value also in the diagnosis of TLE.**

Keywords: Diffusion, Epilepsy, Imaging, Lateralization, Spectroscopy

1. Introduction

Temporal lobe epilepsy (TLE) is the most common form of partial epilepsy. There are two types of TLE: mesial TLE involves medial or internal structures of the temporal lobe. Seizures often begin in the hippocampus or the surrounding area. Mesial temporal lobe accounts for almost 80% of all temporal lobe seizures. Neocortical or lateral TLE involves the outer temporal lobe [1].

The temporal lobe is the most epileptogenic region of the brain. TLE is the most frequent cause of focal and refractory seizures. Mesial temporal sclerosis is the pathologic finding in 65% of temporal lobectomy specimens from adults with TLE. Mesial temporal sclerosis usually starts at the age of 10 or 20 but can also start at any age. Patients have mostly a history of seizures with fever or an injury to the brain in their early life. The majority of temporal lobe seizures originates in the mesial temporal structures, primarily in the hippocampus, parahippocampal gyrus, and amygdala [2].

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that provides metabolic

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information about the brain tissue; and it shows biochemical information and can detect metabolic abnormalities before the appearance of structural lesions, so it is higher than the conventional MRI [3].

MRS has at least two major roles in the evaluation of epileptic patients. First, MRS can help to understand the interaction between seizures and metabolic function. Thus, MRS is particularly interesting for basic science studies of seizures and epilepsy. Second, MRS can explain the nature of seizure control and/or provide localization information by measuring metabolic changes. So, MRS can be used as a powerful complementary technique to structural MRI for the diagnosis and assessment of response to therapy, and measurement of disease progression [4].

Diffusion tensor imaging (DTI) is an MRI technique that uses anisotropic diffusion to estimate the axon (white matter) organization in the brain. Potential clinical applications of DTI started since 1990. Furthermore, diffusion is truly a three-dimensional process. Hence, molecular mobility in tissues may not be the same in all directions. This anisotropy may result from physical arrangement of the medium (such as in liquid crystals) or the obstacles that limit molecular movement in some directions. As diffusion is encoded in the MRI signal by using magnetic field gradient pulses, the effect of diffusion anisotropy can be easily detected by observing variations in diffusion measurements when the direction of the gradient pulses is changed. This is a unique, powerful feature not found with usual MRI parameters [5].

DTI helps some patients with the opportunity to receive suitable treatment at the time when the brain tissue is still salvageable [6]. The aim of this work was to compare the lateralizing ability of MRS and DTI in patients with TLE.

2. Patients and methods

This case–control study was conducted at Menoufia University Hospital on 50 participants selected from Menoufia Neurology Department. The included participants were divided into two equal groups with 25 cases in each: group 1: 25 patients with TLE and group 2: 25 normal controls.

Informed consent was taken from all patients regarding information on the device and its possible complication. Approval was obtained from the IRB (Institutional Review Board) in Menoufia University before starting data collection.

Patient selection: all participants have fulfilled the following criteria.

2.1. Inclusion criteria

Age group: all ages were included. Patients diagnosed clinically with TLE based on a detailed description of seizures from prompt eyewitnesses. The diagnosis is based on the (2017) ILAE Classification of Seizures and Epilepsies. Both sexes were included.

2.2. Exclusion criteria

Other types of epilepsy. Any structure lesion causing epilepsy like ischemia, tumors, and any malformations, presence of psychiatric illness, and patients with current history of alcohol or substance abuse.

2.3. Study procedures

All participants were subjected to the following:

Clinical assessment: history taking, medical and neurological examination according to neurology and epilepsy sheet.

Neurophysiology [electroencephalogram (EEG)] assessment: interictal EEG was performed for all participants. Interracial EEG was obtained in the intervals between clinical attacks. It is the most frequent recording type in clinical practice.

Radiological assessment: noncontrast MRI of the brain, T1-weighted images (axial, sagittal), T2-weighted images (axial, coronal), and fluid-attenuated inversion recovery sequence (axial, coronal). MRS was also done at the 1.5 T super conducting system. Spectroscopy is a series of tests that are added to MRI scan of the brain to analyze molecules and measure different metabolites or products of metabolism such as amino acids, lipids, lactate, alanine N-acetyl aspartate, choline, and creatine, GE Optima MR450W 1.5 T MRI. DTI is the MRI technique that uses anisotropic diffusion to estimate brain white matter.

2.4. Laboratory investigations

Routine laboratory investigations such as complete blood count, liver enzymes, renal function tests, blood sugar, and serum electrolytes (Na, K, Mg, Ca) were done.

2.5. Statistical analysis

Data were collected, revised, then extracted, and coded in an Excel sheet. The coded data were analyzed using the Statistical Package for the Social

Sciences (SPSS, IBM Corp., Armonk, New York, USA), version 26. The analyzed data was presented in suitable tables and graphs using mean ± SD for continuous variables, frequency, and percentage for categorical variables. Suitable analyses were conducted according to the type of data obtained for each variable: independent two-sample t test was used to analyze continuous variable differences across independent two groups after confirming distribution normality, while χ^2 test was used to examine the relationship between two qualitative variables. Fisher's exact test was used to examine the relationship between two qualitative variables when the χ^2 test assumptions were violated (the expected count is < 5 in >20% of cells). To estimate the diagnostic ability of new radiological tools compared with traditional tools, the following indicators were calculated: Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. In addition, the receiver-operating characteristic (ROC) curve was drawn for each parameter, the area under the ROC curves were calculated, and the statistical differences between the area under the ROC curves and 0.5 were calculated and tested for significance. All tests of significance were conducted at 0.05 level of significance.

3. Results

The study recruited 50 participants assigned into two groups: the first group included 25 epileptic cases and the second group included 25 control patients.

The study recruited 50 participant assigned into two groups: the first group included 25 epileptic cases and the second group included 25 normal controls. Group patients included 12 (48%) males and 13 (52%) females and normal controls included 15 (60%) males and 10 (40%) females. Age showed a mean ± SD of 24.22 ± 9.7 years (Table 1).

Table 1. Demographic and historical data of the groups.

Variables	Cases (*N* = 25) [*n* (%)]		Control (*N* = 25) [*n* (%)]		*P* value
Sex					
Male	12 (48)		15 (60)		0.39
Female	13 (52)		10 (40)		
Family history					
Yes	17 (68)		9 (36)		0.01*
No	8 (32)		16 (64)		
Febrile convulsion					
Yes	15 (60)		7 (28)		0.02*
No	10 (40)		18 (72)		
Variables	Mean	SD	Mean	SD	*P* value
Age	19.8	11.5	24.6	10.4	0.132

χ^2 test was used for sex comparisons. Independent samples t test was used for mean age comparison.
*Significant *P* value at 0.05 level of significance.

Table 2. Diagnostic tools utilized among the epileptic group.

Diagnostic tools among cases (*N* = 25)	*n* (%)
Semiology	
Focal unaware	18 (72.0)
Focal unaware and focal to bilateral tonic–clonic	7 (28.0)
EEG	
Bilateral temporal epileptic tendency to be generalized	1 (4.0)
Left frontotemporal epilepsy	1 (4.0)
Left temporal epileptic activity	2 (8.0)
Left temporal epileptic activity with tendency to be generalized	1 (4.0)
Right temporal epileptic activity	2 (8.0)
Subcortical changes	1 (4.0)
No changes	17 (68.0)
Hippocampal and sclerosis normal MRI	
No changes	25 (100)
Epilepsy protocol MRI	
Mild to moderate right hippocampal sclerosis	5 (20)
Mild to moderate left hippocampal sclerosis	2 (8.0)
No changes	18 (72.0)

EEG, electroencephalography.

Tables 2 and 3 compared all diagnostic tools, in addition to semiology regarding sensitivity, specificity, positive and negative predictive values, and finally, accuracy.

Semiology showed the highest and the most perfect diagnostic ability indices for epilepsy (100%), followed by MRS (accuracy = 92%) and DTI difference more than or equal to 0.014 (accuracy = 86%). However, EEG and MRI with or without an epilepsy

Table 3. Clinical and radiological data of the study groups.

Variables	Cases (*N* = 25) [*n* (%)]	Control (*N* = 25) [*n* (%)]	*P* value
Semiology			
Positive	25 (100)	0	<0.001*
Negative	0	25 (100)	
EEG			
Positive	8 (32)	0	0.004*
Negative	17 (68)	25 (100)	
MRI			
Positive	0	0	NA
Negative	25 (100)	25 (100)	
Epilepsy protocol			
Positive	7 (28)	0	0.01*
Negative	18 (72)	25 (100)	
MRS			
Positive	21 (84)	0	<0.001*
Negative	4 (16)	25 (100)	
DTI			
Positive	18 (72)	0	<0.001*
Negative	7 (28)	25 (100)	

DTI, diffusion tensor imaging; EEG, electroencephalography; MRS, magnetic resonance spectroscopy.
χ^2 test or Fisher's exact text was used for the above comparisons.
*Significant *P* value at 0.05 level of significance.

Table 4. Comparisons between area under the receiver-operating characteristic curves of the clinical and diagnostic tools utilized in the study.

Variables	Sensitivity	Specificity	PPV	NPV	Accuracy
Semiology	100	100	100	100	100
EEG	32	100	100	59.5	66
MRI	0	100	100	50	50
Epilepsy protocol	28	100	100	58.1	64
MRS	84	100	100	86.2	92
DTI difference $\geq$0.014	72	100	100	78.1	86
MRS + DTI difference $\geq$0.014	84	100	100	86.2	92
MRS + MRI	84	100	100	86.2	92
MRS + EEG	84	100	100	86.2	92

DTI, diffusion tensor imaging; EEG, electroencephalography; MRS, magnetic resonance spectroscopy; NPV, negative predictive value; PPV, positive predictive value.

protocol showed the lowest values (66 and 50%, respectively).

Furthermore, the addition of DTI difference, MRI, or EEG to MRS did not improve the diagnostic accuracy and remained the same (accuracy = 92%) (Table 4).

Table 5 shows the extended comparisons between the diagnostic tools to include area under the ROC curves. Semiology exerted an area of 1.00, which is the maximum area, followed by MRS [area under curve (AUC) = 0.92], and DTI difference (AUC = 0.89). However, the DTI difference variable treated as the binomial had an AUC of 0.86 for values equal to or greater than 0.014.

4. Discussion

In this work methodology was a good tool to investigate TLE by using 50 participants assigned into two groups.

Men more frequently experienced secondarily generalized tonic–clonic seizures, while women had isolated auras and lateralized EEG seizure pattern more often. Recently, Janszky et al. [7] have found that in men with right-sided epilepsy, seizures began earlier than in those with left-sided discharges, whereas women showed the opposite trend.

Table 5. Statistical difference between area under the receiver-operating characteristic curves of all diagnostic tools and semiology receiver-operating characteristic curve.

Relative to semiology	Difference in AUC	SE	95% CI	*P* value
EEG	0.34	0.22	0.25–0.43	<0.001*
MRI	0.36	0.21	0.27–0.45	<0.001*
Epilepsy protocol	0.36	0.21	0.27–0.45	<0.001*
MRS	0.08	0.19	0.007–0.15	0.033*
DTI difference	0.108	0.22	0.013–0.20	0.026*
DTI difference $\geq$0.014	0.14	0.21	0.05–0.23	0.002*

95% CI, 95% confidence interval; AUC, area under curve of receiver-operating characteristic curve; DTI, diffusion tensor imaging; EEG, electroencephalography; MRS, magnetic resonance spectroscopy.
*Significantly p value.

Considering age, the incidence of epilepsy had bimodal distribution peaking at the extremes of life. Incidence was greater in younger and older age groups, Hauser et al. [8]. TLE has been reported in adults with a familiar history of epilepsy (mean age of onset: 25.5; range: 11–45 years).

The family history of epilepsy, history of prolonged febrile seizure or other insults such as trauma and infection in early life were typical of the syndrome of mesial TLE [9].

Semiology in our study showed the highest and the most perfect diagnostic ability indices for epilepsy (100%). This was in accordance with the self-organizing map method, which was applied to markers to provide predictive methods for mesial TLE lateralization. The self-organizing map clustered all clinical attributes correctly with 100% accuracy and sensitivity for both the left and right mesial TLE. Among the clinical markers, seizure semiology and interracial-irrelative zone are the most sensitive attribute for the left-mesial TLE group lateralization [10].

In our study, all the patients have shown symptoms that ranged from focal unaware (72%) to focal to bilateral tonic–clonic (28%).

EEG was needed for accurate lateralization and localization of the seizure onset in TLE. Standard EEG can detect up to 58% of all interracial spikes; therefore, additional 'nonstandard' electrodes can be used to further evaluate the EEG abnormalities. Ictal rhythms in TLE includes background attenuation, irregular 2–5 Hz lateralized activity, and 5–10 Hz sinusoidal waves or repetitive epileptiform potentials [11].

In this study, EEG showed the following findings among the cases [bilateral temporal epileptic tendency to be generalized (one case), left frontotemporal epilepsy (one case), left temporal epileptic activity in two cases, left temporal epileptic activity with tendency to be generalized (one case), right temporal epileptic activity (two cases), subcortical changes (one case)], and no changes in 17 cases.

The Ercan et al. [12] study included unilateral TLE patients according to EEG findings. Patients were classified into two groups according to EEG lateralization: right TLE ($n = 7$) and left TLE ($n = 7$).

Also in the Aun et al. [13] study, 30 cases have been examined having abnormal EEG, 17 cases with right-sided EEG, 11 cases with left-sided EEG, and two cases of bilateral EEG abnormalities.

The results from an individual's clinical and neurophysiological examinations that are both interpretable and congruent were regarded as the 'gold standard' for localizing the epileptogenic area. This usually involves a combination of video monitoring and EEG recording, which is generally performed in a hospital setting often for a prolonged period of time and after reduction of medication [13].

Furthermore, in some patients with no clear localization or lateralization of the epileptogenic area, an invasive neurophysiological approach is required for further clarification. This is often the case in patients who are either diagnosed to have bilateral TLE or who have shown conflicting clinical and EEG-localizing features [14].

In spite of the high tissue characterization and multiplanar capability of MRI in the evaluation of seizure patients, some patients with TLE still seem to have normal MR appearance, that is to say negative MRI. The search for a highly accurate, noninvasive method for localization of seizure focus led to investigate the usefulness of MRS in seizure field. The MRS is a noninvasive modality that provides metabolic information about the brain tissue and enables tissue characterization on a biochemical level surpassing that of the conventional MRI. MRS is also able to detect abnormalities that are invisible to conventional MRI, as metabolic abnormalities often precede structural changes [13].

In our study, MRS accuracy was 92% which was in agreement with several studies where MRS results have been in the range of 86–100% [15].

Also, in the study by Park et al. [16] the sensitivity of MRS was 85% each in the lateralization of the ipsilateral lesion side. It revealed an abnormality in the affected hippocampal region in only 28 (85%) of the 33 patients with hippocampal sclerosis.

Supporting our study, Fountas and Pinnell [17] showed that the sensitivity of proton MRS was 100%, its specificity was 80%, its positive predictive value was 87%, and its negative predictive value was 100%.

While in the Ercan et al. [12] study, individual volumetric measurements provided accurate lateralization in 85% of the patients, spectroscopy in 57%, and DTI in 57%. Higher lateralization ratios were acquired combining volumetry-spectroscopy (85%), spectroscopy-DTI (85%), and volumetry-DTI (100%).

On comparing lateralization of TLE by MRS with the gold standard EEG, they found that EEG and MRS results were highly concordant [13].

DTI is a newer method that has not been incorporated in routine clinical practice. Nevertheless, attempts have been made to use DTI data for distinguishing left TLE from right TLE. In this study, DTI difference more than or equal to 0.014 accuracy was 86%. In accordance with our study, Ahmadi and Jullien [18] reported 90% accuracy, Doelken et al. [19] reported 91% accuracy, while Concha et al. [20] reported 87% accuracy. However in Pustina et al. [15] study, the success rate of 71% when using only DTI asymmetries is lower than these reports, a finding that may again be related to DTI processing steps.

DTI helps some patients with the opportunity to receive suitable treatment at the time when the brain tissue is still salvageable [15].

Furthermore, this study showed that semiology was the best and the perfect mean for the diagnosis of TLE.

MRS has the highest accuracy (92%), and when added more investigations like DTI, MRI, or EEG it did not increase the accuracy.

5. Conclusion

Semiology showed the highest and the most perfect diagnostic ability indices for epilepsy (100%).

MRS was a highly sensitive tool to predict the TLE and the side of involvement in patients with TLE even in MR-negative patients. It aided in the detection of aberrant spectrums of different brain metabolites. MRS had demonstrated consistent metabolic abnormalities in partial seizures. MRS showed very considerable role (accuracy = 92%).

The DTI difference more than or equal to 0.014 (accuracy = 86%), so it has a high value also in the diagnosis of TLE.

Conflict of interest

There are no conflicts of interest.

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