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Advanced Magnetic Resonance Imaging Techniques in Assessment of Pediatric Patients With Epilepsy

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ABSTRACT

Background: Epilepsy is a neurological condition that is prevalent among individuals of all ages, races, social classes, and geographical locations. This research aimed to assess the value of arterial spin labeling (ASL), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS) as novel MRI approaches, in detecting the epileptogenic zone in pediatric patients with epilepsy of unknown cause who had normal conventional magnetic resonance imaging.

Methods: This prospective case-control research involved 60 patients aged from two to 18 years, both sexes, with intractable epilepsy with unknown cause while conventional magnetic resonance imaging was normal and 60 healthy volunteers of nearly similar ages as control group. All patients were subjected to MRS, DTI and ASL perfusion.

Results: Both the epilepsy and control groups showed significant differences in hippocampal fractional anisotropy, mean diffusivity (MD), ASL, NAA/CHO+Cr, or NAA/CR ($P<0.001$). The hippocampus's fractional anisotropy (FA) and MD showed extremely strong agreement with NAA/Cr and NAA/Cho + Cr, ASL showed good agreement with both of these parameters, while MRS and ASL parameters showed poor agreement with DTI parameters. There was poor agreement between MRS, DTI and ASL with electroencephalography finding.

Conclusions: By combining MRS, DTI, and ASL, diagnostic accuracy is significantly increased compared to using each sequence individually. This combination also yields great results in localizing and lateralizing of the epileptogenic focus.

Keywords: *Magnetic Resonance spectroscopy , Pediatric, Epilepsy, Diffusion Tensor Imaging, Arterial Spin Labeling*

1. INTRODUCTION

Epilepsy is a prevalent neurological illness that can impact individuals from all age groups, races, socioeconomic statuses, and geographic regions [1].

Seizures can be classified based on onset into focal, generalized, or unknown types. Focal seizures are further divided into those with retained awareness and impaired awareness. Generalized seizures include motor and non-motor (absence) types [2].

Partial seizures that affect only a portion of the brain such as the temporal, frontal, parietal, or occipital lobes, affect half of all epileptic patients. The great majority of epileptic cases are classified as temporal lobe epilepsy (TLE), and mesial TLE is the most common subtype of TLE. About 60% to 70% of people with TLE have mesial temporal sclerosis (MTS) [3].

Brain imaging is essential for evaluating patients with epilepsy to identify underlying structural brain abnormalities such as tumors, vascular diseases, or infections. Neuroimaging methods include non-contrast computed tomography (CT), structural and functional MR imaging (fMRI), magnetic resonance spectroscopy (MRS), electroencephalography (EEG) in conjunction with fMRI, positron emission tomography (PET), and both intraictal and ictal single-photon emission tomography (SPECT) [4].

MRI is a crucial diagnostic tool in epilepsy assessment. Its primary indications are for etiological and differential diagnosis, follow-up for known disorders, and pre-surgical evaluation [5].

Metabolic abnormalities in a variety of neurological illnesses, such as TLE, can be investigated with the help of MRS, which offers non-invasive biochemical information [6].

Diffusion tensor imaging (DTI) has the potential to enhance white matter fiber tract visualization by determining the orientation, anisotropy, and direction of the fiber bundles by comparing the mobility of water molecules along and perpendicular to them [7].

The arterial spin labeling (ASL) product sequence is available on the majority of MRI equipment. It is a non-invasive technique with scanning times that are practical for clinical use. Many forms of epilepsy have shown improvement after implementing ASL, including those affecting the frontal and temporal lobes [8].

Neuroimaging techniques that can detect changes in brain function include fluorodeoxyglucose positron emission tomography (FDG-PET), interictal and ictal single-photon emission tomography (SPECT), and the combination of the two [9].

Our study is considered to be one of the first studies to test combination of MRS, DTI and ASL sequences in diagnosis of MRI negative epilepsy.

This study aimed to evaluate the effectiveness of advanced MRI techniques like ASL, MRS, and diffusion tensor imaging in locating the epileptogenic zone in children with MRI negative epilepsy.

2. METHODS

This prospective case control study involved 60 patients aged from two to 18 years old, both sexes, with intractable epilepsy of unknown cause while conventional magnetic resonance imaging was normal. For the imaging studies, all patients were free of medication for at least two weeks, along with sixty healthy people of similar age who served as a control group. The investigation was conducted after the approval of the Ethical Committee unit in our institution. Patient signed informed consent was acquired.

Patients were not included if they had a positive MRI finding for epilepsy such as space occupying lesions or MTS, had a metabolic disease that affects the ratios of cerebral metabolite concentrations (such as diabetes or brain surgery), had a medical condition that would prevent an MRI (such as a metallic prosthesis or artificial pacemaker), in the case of the control group if they had a positive family history for epilepsy.

Every patient underwent a thorough medical history and MRI scan.

Magnetic resonance Examination:

The investigation was conducted at the Radio-diagnosis and medical imaging Department at our hospital' MRI unit utilizing a 1.5 Tesla closed magnet General Electric (GE) Signa Explorer .All patients and volunteers are examined headfirst in supine position, using standard 16-channel head coil with the head maintained in a neutral position. The patient removed all metal objects like pins and earrings. A head support pillow can help the patient stay still as much as possible. Children under the age of 8 were sedated with chloral hydrate during data collection; the dosage was 25 to 50 mg/kg orally 30 minutes before MRI imaging; if needed, half the amount could be given again 30 minutes later. Also, sedation was used in elderly uncooperative children.

Magnetic resonance spectroscopy (MRS):

MRS including short TE (35 ms) and long TE (144 ms) echo acquisitions using a repetition time of 2000 ms, shimming was performed, multi-voxels MR spectroscopy localization, and positioned within both hippocampi.

A number of resonances were detected among the most notable metabolites: N-acetyl aspartate (NAA)–2.02 ppm, creatine (Cr)–3.02 ppm, and choline (3.20 ppm). Quantitative and qualitative analysis were performed on the MRS spectra files to assess lipids, lactate peaks in short TE in each hippocampus, NAA/Cr, and NAA/Cho+Cr using MRI workstation software (advantage window 4.7, GE Medical Systems) for post-processing. Peak calibrations, spectral plotting, baseline correction, phase correction, and baseline alignment were all steps in the post-processing of the spectra. The goal was to remove any draft from the baseline, lower the noise level, and align the peaks. The peak areas of choline, creatine, and N-acetyl aspartate were calculated for each voxel. Taking the integral of NAA and dividing it by the sum of the integrals of Cr + Cho gives us the formula for determining the ratio of NAA to Cr + Cho.

Diffusion tensor imaging (DTI):

We used a 208×170 matrix, 124 0.8 mm thick slices, a 400 ms time inversion, and a 35° flip angle to obtain a sequence of high-resolution 3D T1-weighted spoiled gradient echo pulses. By utilizing the specified parameters: DTI was performed using a single-shot spin-echo echoplanar sequence in 40 encoding directions and a diffusion weighting factor of 800 mm/s.

The following parameters were used: TR= 8000-10000 m.sec., TE= 70-120 m.sec., matrix 128x128mm, FOV: 224 x224mm. Slice thickness was 3 mm. Flip angle was 90 degrees.

After transferring DTIs to the workstation (GE Medical Systems' Advantage Window 4.7), numerous DTI indices, including FA and MD, were created and the images were color coded to resemble maps. The two hippocampi were analyzed by identifying white matter regions and then drawing ROIs within those areas. In order to compare ROIs in one hemisphere with those in the other, DTI values were computed for each ROI.

The color-coded DTI maps were compared to the other side visually to evaluate their quality, and their FA and MD values were compared to the other side quantitatively to make conclusions.

Arterial spin labeling (ASL) perfusion

An imaging sequence for PCASL perfusion was carried out using 2.25 µT RF, which is equivalent to a 90° pulse that lasts 2.6 ms and a gradient of 1.6 mT/m. Using a sinusoidal modulation function and an amplitude modulated variation of the labeling pulse, blood was alternately tagged and untagged. The total duration of the labeling and control pulses was two seconds. Gradient EPI sequence imaging was performed following a post-labeling delay of 1200-1500 ms. A 25 cm field of view (FOV), 64×64 matrix size, 4000 ms time (TR), 90° flip angle, 2 mm slice thickness, and 1 mm inter-slice gap were utilized as acquisition parameters. For both sets of images, TE of 17 and 45 ms were necessary for full k-space imaging. The rCBF perfusion color maps were produced mechanically. The results were evaluated qualitatively using a color-coded map system, with red indicating locations with high perfusion and blue indicating areas with low perfusion. Hypoperfsued focus indicating lateralization of the epileptogenic focus of the affected lobe. The quantitative study of regional cerebral blood flow (rCBF) at ROIs in both hippocampi, which were manually placed using a workstation analysis package with specialized neuroimaging software, measured around $1\times1\times1$ cm^2.

Image interpretation and post processing:

At the workstation (GE Medical Systems' Advantage Window 4.7), post-processing of images was carried out using the produced MRI data. All pulse sequence data was compared to the control group and cross-referenced with clinical data and electroencephalography (EEG) results.

All data were reviewed and analyzed by two experienced neuroradiologists with 9, 10 years of experience in neuroradiology, the final decision was given by athird experienced consultant of neuroradiology who had 15 years of experience in advanced neuroimaging field

who gave his opinion in controversy opinions.

Statistical analysis

SPSS v26 (IBM Inc., Chicago, IL, USA) was employed to conduct statistical analysis. We used an unpaired Student's t-test to compare the two groups' quantitative variables, which were given as means and standard deviations (SD). The percentages and frequencies of the qualitative variables were analyzed using the Chi-square or Fisher's exact test, as appropriate. We used a receiver operating characteristic (ROC) curve to evaluate the diagnostic performance's sensitivity, specificity, PPV, and NPV. The following are the results of the Kappa test: without a value, there is no agreement, moderate agreement (0.0 - 0.20), fair agreement (0.21-0.40), moderate to strong agreement (0.41-0.60), significant agreement (0.61-0.80), and near entire agreement (0.81-0.00). A two-tailed P value below 0.05 was considered statistically significant.

3. RESULTS

There was no statistically significant difference in age or sex between the epileptic patients and the controls. **Table 1**

Table 1: Demographic data of the studied groups

		Control group (n=60)	Epilepsy group (n=60)	P
Age (years)		9.22± 3.51	10.17±3.57	**0.131**
Sex	**Male**	33(55.0%)	32(53.3%)	**0.855**
	Female	27(45.0%)	28(46.7%)	

Data are presented as mean ± SD or frequency (%).

The average age at which epileptic symptoms first appeared was 6.90±2.47 years in patients with epilepsy. With a median of 7 days, the latest attack ranged from 2 to 14 days. Among the patients surveyed, 28 (47.67%) reported attacks monthly, 26 (43.3%) reported attacks sporadic , and 6 (10%) reported attacks annually. The median of disease duration was three years. 21 (35%) of cases had positive family history. Regarding EEG finding, 25 patients (41.7%) had right sided epileptogenic focus in EEG, 16 (26.7%) had left-sided focus, 30% of cases showed indeterminate EEG and one patient showed bilateral epileptogenic foci. **Table 2**

Table 2: Epilepsy patients' clinical data and electroencephalogram results

		N= 60
Age of onset (years)		6.90± 2.47
Last attack (days)		5.97± 4.39
Frequency of attack	**Monthly**	28(46.7%)
	Sporadic	26(43.3%)
	Yearly	6(10.0%)
Disease duration (years)		3.25± 1.83
Family history		21(35.0%)
EEG finding		
Right		25(41.7%)
Left		16(26.7%)
Bilateral		1(1.7%)
Indeterminate		18(30.0%)

Data are presented as mean ± SD or frequency (%). ECG: Electrocardiogram.

The results of the MRS assessment for NAA/Cho + Cr and NAA/Cr were found to be significantly different across the groups (P<0.001). There was a significant difference in hippocampal fractional anisotropy and mean diffusivity between the studied groups that were evaluated by DTI. All of the groups that were studied showed a statistically significant variation in their ASL values (P<0.001). **Table 3**

Table 3: Comparison of NAA/CHO+ Cr and NAA/Cr, hippocampus fractional anisotropy and mean diffusivity and ASL between the studied groups

	NAA/CHO+ Cr	NAA/Cr
Control group (n=60)	1.10±0.23	2.37±0.51
Epilepsy group (n=60)	0.75±0.15	1.70±0.40
P-value	**<0.001***	**<0.001***
	Hippocampus FA	**MD**
Control group (n=60)	0.28±0.03	7.22±0.35
Epilepsy group (n=60)	0.18±0.03	7.92±0.63
P-value	**<0.001***	**<0.001***
	ASL	
Control group (n=60)	65.09±5.85	
Epilepsy group (n=60)	49.56±6.78	
P-value	**<0.001***	

Data are presented as mean ± SD. * Significant p value <0.05, FA: fractional anisotropy, NAA: N –acetyl aspartate, Cho: Choline, Cr: Creatine, MD: Mean diffusivity, ASL: arterial spin labeling.

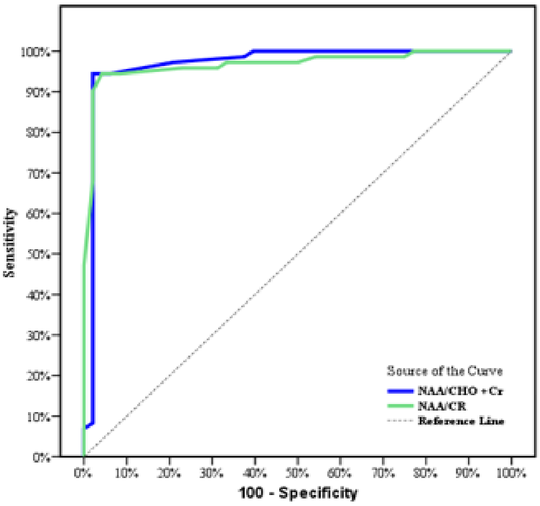
The right and left NAA/CHO+ Cr, NAA/CR, hippocampus fractional anisotropy, MD, and ASL, in both control group and the epilepsy group, did not differ significantly (P>0.05). **Table 4**

Table 4: Comparison between right and left NAA/CHO+ Cr and NAA/Cr, hippocampus fractional anisotropy and mean diffusivity and ASL in the studied groups

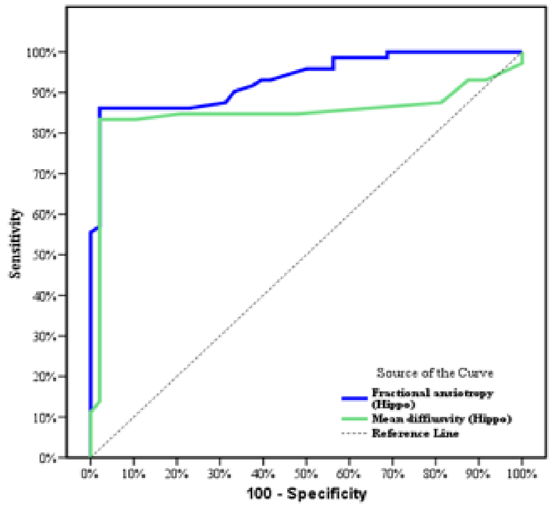
	Control group (n=60)	Epilepsy group (n=60)
NAA/CHO +Cr		
Right	1.09±0.24	0.74±0.31
Left	1.11±0.24	0.76±0.24
P-value	0.163	0.621
NAA/Cr		
Right	2.37±0.54	1.61±0.69
Left	2.38±0.50	1.79±0.68
P-value	0.787	0.158
Hippocampus Fractional anisotropy		
Right	0.28±0.03	0.18±0.05
Left	0.28±0.03	0.19±0.04
P-value	0.841	0.359
Hippo. MD (×x10^{-3})		
Right	7.20±0.34	7.94±1.0
Left	7.24±0.38	7.92±1.08
P-value	0.064	0.935
ASL		
Right	64.98±5.73	48.52±12.69
Left	65.32±6.07	50.60±11.71
P-value	0.069	0.311

Data are presented as mean ± SD. * Significant p value <0.05, FA: fractional anisotropy, NAA: N –acetyl aspartate, Cho: Choline, Cr: Creatine, MD: Mean diffusivity, ASL: arterial spin labeling.

The NAA/Cr value, when evaluated using MRS, has a sensitivity of 95.38 and a specificity of 77.08 when the cut off value is ≤1.7, whereas the NAA/Cho + Cr value, when evaluated using MRS, has a sensitivity of 94.44 and a specificity of 97.9 when the cut off value is ≤0.69. In terms of DTI evaluation, it showed that hippocampus FA had a sensitivity of 86.11 and a specificity of 97.92, with a cutoff value of ≤0.196., while value of hippocampus mean diffusivity with cut off value >7.6, sensitivity 76.39 and specificity 93.75. Regarding ASL findings, ASL value with cutoff value was 49, sensitivity 94.44 and specificity 91.67. **Figure 1**



(A)



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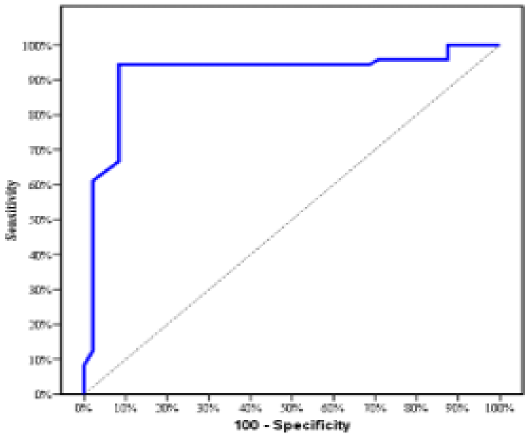


(C)

Figure 1: ROC curve for (A) NAA/CHO +Cr and NAA/CR, (B) Hippocampus fractional anisotropy and mean diffusivity and (C) arterial spin labeling in lateralization and localization of epileptic focus

Reports from MRS indicated that 27 patients had right-sided epileptic focus, and 18 patients had left-sided epileptic focus; 12 patients had bilateral epileptic focus, while the remaining 3 patients were indeterminate. Based on the results of the DTI, 26 patients had right sided foci, 19 on the left side, 9 on both sides, and 6 were classified as indeterminate. A total of 25 patients exhibited right-sided epileptic focus, 18 displayed left-sided epileptic focus, 9 exhibited bilateral epileptic focus, and 8 remaining were indeterminate according to the ASL findings. There were 25 right-sided foci, 16 left-sided foci, 1 bilateral focal, while the remaining 18 patients were indeterminate in the electroencephalogram data. **Figure2**

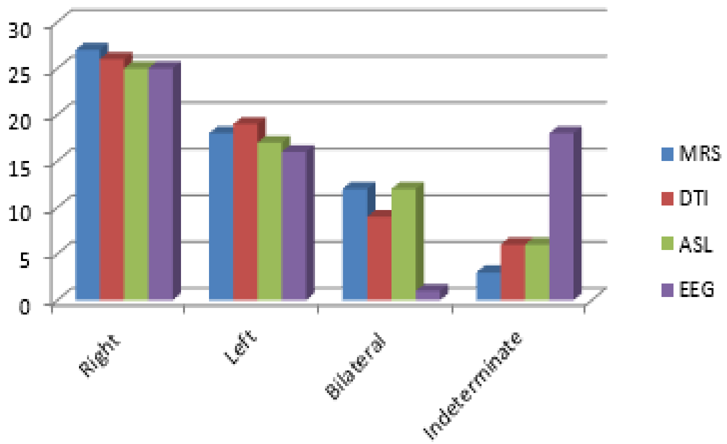


Figure 2: Lateralization of epileptic focus among studied patients using MRS ,DTI , ASL and EEG

Very good agreement was found between both MRS parameters as well as both DTI parameters and while there was good agreement between both ASL and MRS finding, despite poor agreement with MRS and ASL characteristics with DTI parameters. **Table 5**

Table 5: Agreement between MRS, DTI and ASL

	Kappa	P value	Level of agreement
NAA/CHO +Cr vs NAA/CR	0.893	**<0.001***	Very good agreement
NAA/CHO +Cr vs Fractional anisotropy (Hippo)	-0.071	0.554	Poor agreement
NAA/CHO +Cr vs Mean diffusivity (Hippo)	-0.078	0.486	Poor agreement
NAA/CHO +Cr vs Laterality in ASL	0.733	**<0.001***	Good agreement
NAA/CR vs Fractional anisotropy (Hippo)	-0.100	0.436	Poor agreement
NAA/CR vs Mean diffusivity (Hippo)	-0.114	0.360	Poor agreement
NAA/CR vs Laterality in ASL	0.712	**<0.001***	Good agreement
FA (Hippo) vs MD(Hippo)	0.839	**<0.001***	Very good agreement
FA (Hippo) vs Laterality in ASL	-0.111	0.389	Poor agreement
MD (Hippo)vs Laterality in ASL	-0.129	0.311	Poor agreement

* Significant p value <0.05, <0.20: poor, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: good, 0.81-1.00: very good, MRS: Magnetic resonance spectroscopy, DTI: Diffusion tensor imaging, FA: fractional anisotropy, NAA: N –acetyl aspartate, Cho: Choline, Cr: Creatine, MD: Mean diffusivity, ASL: arterial spin labeling.

There was poor agreement between MRS, DTI, ASL with EEG finding. **Table 6**

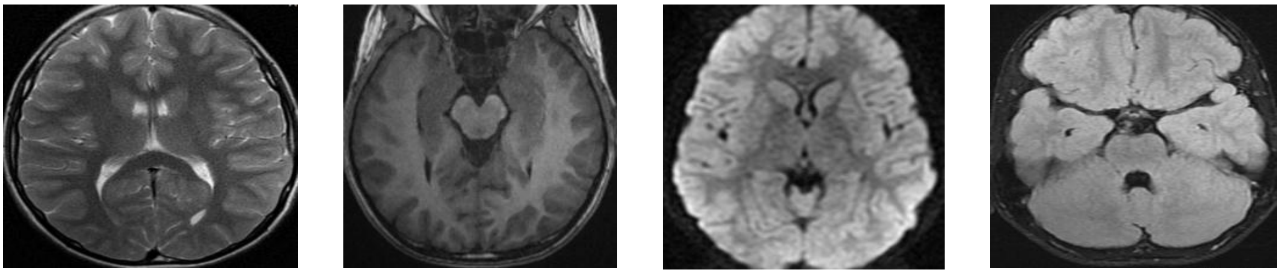
Table 6: Agreement (sensitivity, specificity and accuracy) for different parameters with EEG finding

		EEG finding		Sensitivity	Specificity	PPV	NPV	Accuracy
		Normal (n = 18	**Abnormal (n = 42)**					
NAA/CHO +Cr	**Normal**	0(0.0%)	3(7.1%)	92.86	0.0	68.42	0.0	65.0
	Abnormal	18(100.0%)	39(92.9%)					

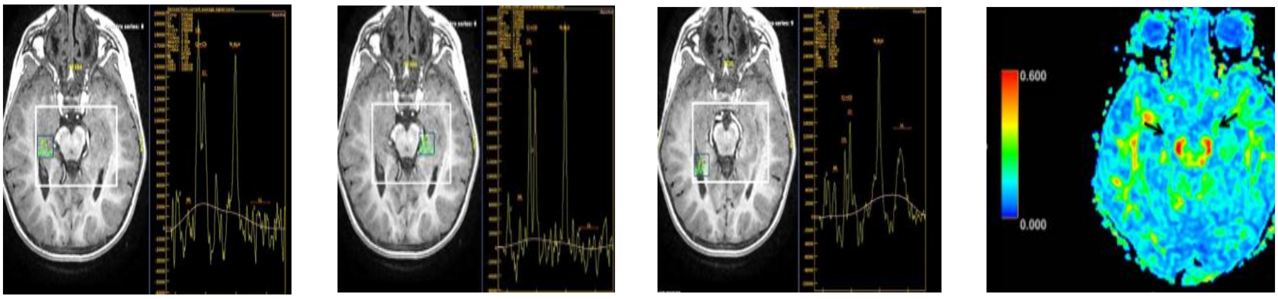
κ (Level of agreement)		-0.094(0.547) (Poor agreement)						
NAA/CR	**Normal**	0(0.0%)	5(11.9%)	88.10	0.0	67.27	0.0	61.67
	Abnormal	18(100.0%)	37(88.1%)					
κ (Level of agreement)		-0.150(0.309) (Poor agreement)						
FA (Hippo)	**Normal**	0(0.0%)	6(14.3%)	85.71	0.0	66.67	0.0	60.0
	Abnormal	18(100.0%)	36(85.7%)					
κ (Level of agreement)		-0.176(0.165) (Poor agreement)						
MD (Hippo	**Normal**	0(0.0%)	8(19.0%)	80.95	0.0	65.38	0.0	56.67
	Abnormal	18(100.0%)	34(81.0%)					
κ (Level of agreement)		-0.226(0.091) (Poor agreement)						
Laterality in ASL	**Normal**	1(5.6%)	5(11.9%)	88.10	5.56	68.52	16.67	63.33
	Abnormal	17(94.4%)	37(88.1%)					
κ (Level of agreement)		-0.078(0.658) (Poor agreement)						

* Significant p value <0.05, <0.20: poor, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: good, 0.81-1.00: very good, PPV: positive predictive value, NPV: negative predictive value, MRS: Magnetic resonance spectroscopy, DTI: Diffusion tensor imaging, FA: fractional anisotropy, NAA: N –acetyl aspartate, Cho: Choline, Cr: Creatine, MD: Mean diffusivity, ASL: arterial spin labeling.

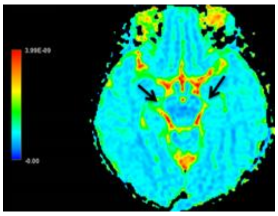
Case 1: A male patient, aged 10, appeared with unresponsive focal seizures; the first attack occurred when he was six years old, and the kid experiences seizures once a month, last attack was 3 days ago, underwent conventional MRI scan that revealed no gross pathological abnormalities, EEG was normal, while advanced MRI imaging (MRS, DTI and ASL) revealed the following changes. **Figure 3**



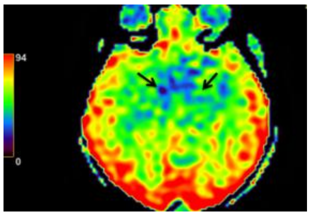
(A) **(B)** **(C)** **(D)**



(E) **(F)** **(G)** **(H)**



(I)

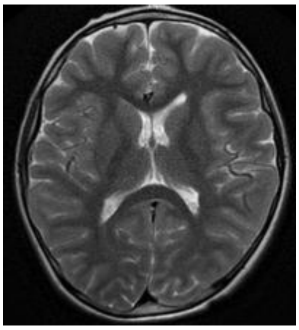


(J)

Figure 3: The structural magnetic resonance images, which comprise axial T2WI (A), axial 3D T1WI (B), axial DWI (C), and axial FLAIR (D), the results are negative , the MV 1H-MRS image maps are shown in (E, F and G). The MRS spectra of the right and left temporal lobes reflect the decrease in NAA/(Cho+Cr) and (NAA/Cr) ratios in the zone of epileptogenic activity in right temporal lobe, long TE on the right temporal lobe (E) NAA/(Cho+Cr) and (NAA/Cr measuring about 0.53 and 1.2, respectively, and on the left temporal lobe (F) measuring about 0.72 and 1.7, respectively with increased lipids at short TE at right temporal lobe (G) the left temporal lobe showed a normal FA value of 0.217 and the right temporal lobe had a focal drop of 0.174, as seen by the black arrows on the FA map (H), while MD map (I) revealed focal increase in the MD value in right temporal lobe measuring 8.6× 10–3 m^2 /sec with normal value at left temporal lobe measuring 7.1× 10–3 m^{-2} /sec (black arrows), the ASL-MRI color-coded cerebral perfusion map (J) shows areas of hypoperfusion in the right temporal lobe with a rCBF of approximately 47 ml/100 g/min; in contrast, the left temporal lobe shows no perfusion abnormalities with a rCBF of 75 ml/100 g/min (black arrows)

Advanced MRI imaging techniques (MRS, DTI and ASL) are in favor of right temporal lobe neuronal changes denoting laterality of epilepsy towards right side, associated with increased lipids/lactate on right side denoting recent seizures/non controlled seizures.

Case 2: A The 12-year-old male patient came in complaining of focal seizures that were not improving despite medical intervention. His first seizure occurred when he was 8 years old, and he has a monthly attack frequency, last attack was two weeks ago , underwent conventional MRI scan that revealed no gross pathological abnormalities, EEG was normal , while advanced MRI imaging (MRS ,DTI and ASL) revealed the following changes. **Figure 4**



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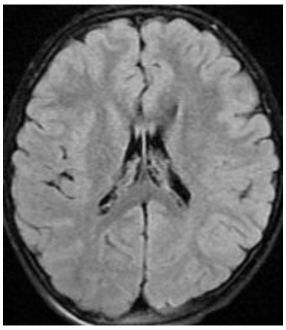

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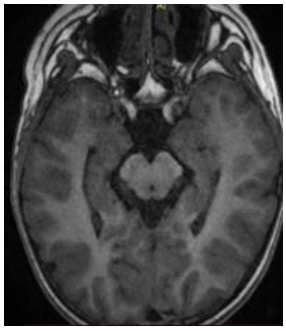

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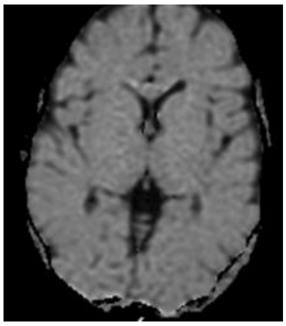

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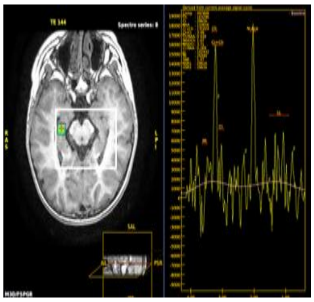

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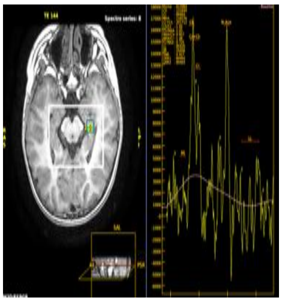

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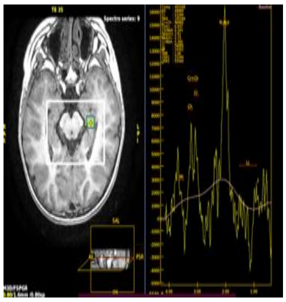

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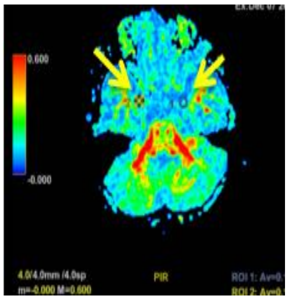
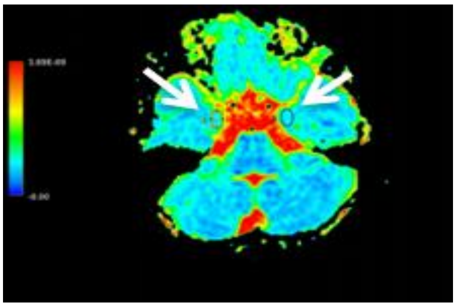
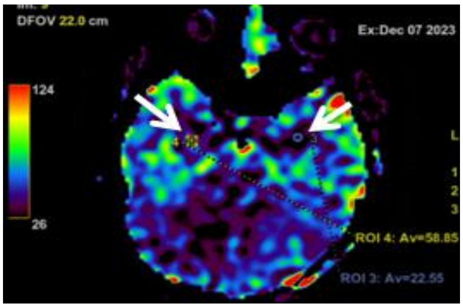


(H)



(I)

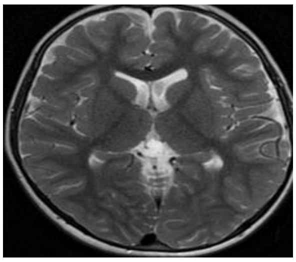


(J)

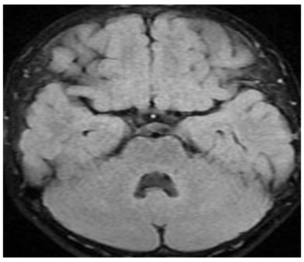
Figure 4: The structural MR images, including axial T2WI (A), axial FLAIR (B), axial 3D T1WI (C), axial DWI (D), all are unremarkable and negative, the MV 1H-MRS picture maps are demonstrated in (E, F and G). The MRS spectra of the right and left temporal lobes reflect the decrease in NAA/(Cho+Cr) and (NAA/Cr) ratios in the zone of epileptogenic activity in left temporal lobe, on the right temporal lobe (E) measuring about 0.8 and 1.6, respectively, and on the left temporal lobe (F) measuring about 0.59 and 1.3, respectively with increased lipids at short TE at left temporal lobe (G), DTI: The FA map (H) revealed focal decrease in the FA value in left temporal lobe measuring 0.1 53 with normal value at right temporal lobe measuring 0.170(Yellow arrows) , while MD map (I) revealed focal increase in the MD value in left temporal lobe measuring 9.27× 10–3 m2 /sec with normal value at right temporal lobe measuring 7.04× 10–3 m.2 /sec(White arrows), The ASL-MRI color-coded cerebral perfusion map (J) reveals foci of hypoperfusion of left temporal lobe with rCBF measuring about 22.5 ml/100 g/min, while no perfusion abnormality on right temporal lobe measuring 58.8 ml/100 g/min(white arrow)

Advanced MRI imaging techniques (MRS, DTI and ASL) are in favor of left temporal lobe neuronal changes denoting laterality of epilepsy towards left side. associated with increased lipids/lactate on left side denoting recent seizures/non controlled seizures.

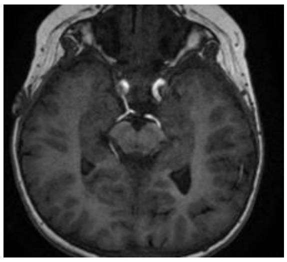
Case 3: A female patient, aged 7, appeared with unresponsive focal seizures. The patient had her first episode when she was four years old, and the frequency of her seizures is sporadic, last attack was 5 days ago, underwent conventional MRI scan that revealed no gross pathological abnormalities, EEG was normal, while advanced MRI imaging (MRS ,DTI and ASL) revealed the following changes. **Figure 5**



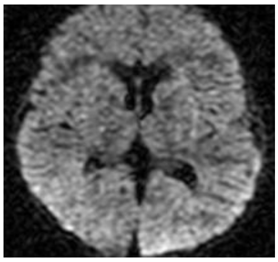
(A)



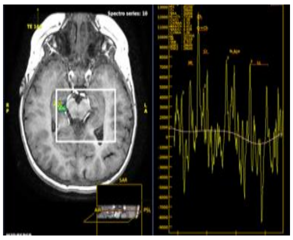
(B)



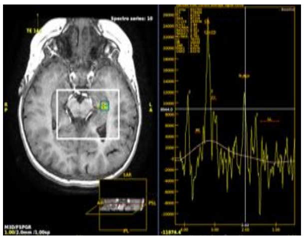
(C)



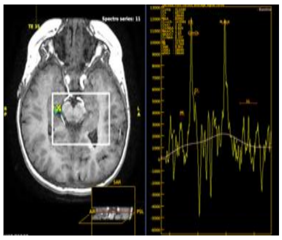
(D)



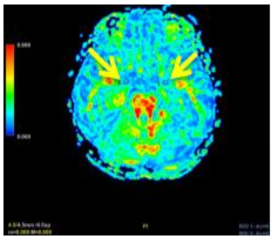
(E)



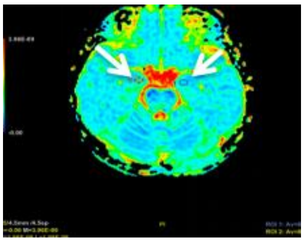
(F)



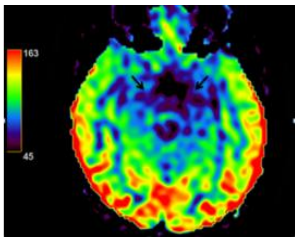
(G)



(H)



(I)



(J)

Figure 5: These structural MR images, which include an axial T2WI (A), an axial FLAIR (B), an axial 3D T1WI (C), and an axial DWI (D), are all negative, (E, F and G) show the MV 1H-MRS image maps, The MRS spectra of the right and left temporal lobes reflect the decrease in NAA/(Cho+Cr) and (NAA/Cr) ratios in the zone of epileptogenic activity in both temporal lobes, on the right temporal lobe (E) measuring about 0.36 and 0.9, respectively, and on the left temporal lobe (F) measuring about 0.49 and 1.6, respectively with increased lipids at short TE at right temporal lobe (G). DTI : According to the FA map (H), there was a localized drop in FA value of 0.127 at the right temporal lobe and 0.119 at the left (Yellow arrows). On the other hand, the MD map (I) showed a localized rise in MD value of 8.10× 10^{-3} m²/sec at the right temporal lobe and 8.85× 10^{-3} m²/sec at the left (White arrows). The ASL-MRI color-coded cerebral perfusion map (J) shows areas of left temporal lobe hypoperfusion with rCBF values of around 22.5 ml/100 g/min; on the other hand, there is no perfusion abnormalities in the right temporal lobe with 58.8 ml/100 g/min (Black arrows)

Advanced MRI imaging techniques (MRS and DTI) are in favor of bilateral temporal lobe neuronal changes associated with increased lipids/lactate on left side denoting recent seizures/non controlled seizures. While ASL finding were non-specific.

4. DISCUSSION

Approximately 50 million individuals worldwide are affected by epilepsy, which is one of the most common neurological disorders. For this reason, a reliable diagnosis is of major importance [10].

We found that, relative to the control group, the mean peak ratios of NAA/(Cho + Cr) and NAA/Cr in the area that has been suggested as a focal epileptogenic activity were substantially lower. The epileptogenic focus was better localized and lateralized with the use of magnetic resonance imaging (MRS), as diagnostic tool. In the right hippocampus, the mean ± SD of NAA/ (Cho + Cr) peaks in the patient group was 0.74±0.31, while in the left hippocampus, it was 0.76±0.24. that was in line with Aydin, et al. [11] who revealed that the mean ± SD of NAA/(Cho + Cr) peaks in the right hippocampi of the patient group was 0.67 ± 0.58, while in the left hippocampi it was 0.73 ± 0.67. Also, our results showed agreement with Liu, et al. [12], who found that the NAA/(Cho + Cr) and NAA/Cr ratios in the temporal pole of the TLES group were lower in the postictal phase than in the healthy control group , 0.796±0.023 and 1.897±0.047 were the mean values of NAA/ (Cho + Cr) and NAA/Cr in the control group, respectively, and 0.606±0.018 and 1.422±0.037 in the patient group.

When we compared the right and left sides of the patient group, we found no significant differences in the values of NAA/Cr and Cho+ Cr, this was in line with Zhang et al. [13] and Voets et al. [14] who found no statistically significant difference between the ipsilateral and contralateral NAA/(Cho + Cr) values in the EEG epileptogenic focus regions of patients with TLE.

The current results showed that the NAA/Cr cutoff value was ≤1.7 with a sensitivity of 94.44% and the NAA/Cho+ Cr cutoff value was ≤0.69 with a sensitivity of 95.64%, this agreed with Aun et al. [15] who found to have an NAA/Cho+ Cr cut-off value of≤0.71 and the study of Mohamed et al. [16] revealed that the cutoff value for NAA/Cho+ Cr was ≤0.76, and the cutoff value for NAA/Cr was ≤ 2.1, with a sensitivity of 96.7% for each.

According to MRS sensitivity, our results matched with the result of Refaat, et al. [17] who revealed that sensitivity of MRS in localization of epileptic focus was 91% and specificity was 82%.

Based on our findings, DTI can be utilized to localize and lateralize the epileptogenic focus using FA and MD. The reason behind this was that the ipsilateral hippocampus showed much lower FA levels and greater MD values. Because FA is a measure of water diffusion and DTI exposes information about the brain's microstructural integrity, it is likely that FA plays a significant role in focus localization.

Regarding to the DTI assessment, our results showed that there was significant difference between both epilepsy and control groups according to FA and MD. This was consistent with the study of Chau Loo Kung. et al. [18] who conducted that compared to controls, patients experiencing seizures had higher mean hippocampus MD ipsilateral to the seizure focus and lower mean hippocampus FA ipsilateral to the seizure focus. That was agreed with the results of Alizadeh et al. [19] who found higher MD values in the ipsilateral hippocampus of TLE patients.

Regarding to sensitivity of DTI in localization of epileptic focus, our results showed that cutoff value of FA was 0.196 with sensitivity 86.11% and specificity 97.92% and the difference in MD in hippocampus showed a cutoff value of 7.6 with sensitivity 76.39% and specificity 93.75% , These results agreed with those of Liu, et al. [12], who demonstrated that FA cutoff value was 0.17 and MD cut off value was 7.3.Furthermore, our findings was in line with those of El-Kapany, et al. [20], who revealed that DTI was sensitive by 72% while its specificity was 100%.

Our research demonstrated that, in the control group, the median ASL was 66.5, while in the epilepsy group, it was 49.25. In terms of ASL, there was a statistically significant difference between the control group and the epilepsy cases. That results were in agreement with those of Mingyuan et al. [21] who found that the healthy control group had an average hippocampal CBF value of 58.82 ± 0.98, while the epileptic group had an average CBF value of 49.12 ± 5.3. As a result, the epilepsy group differed significantly from the healthy control group.

In our results, the epileptic focus was represented by a region of altered perfusion, that happened to be hypoperfused in all cases, which was similar to results of Reda et al.[22] who reported hypoperfusion in all studied cases in their study. Also, this matched with the result of Mohamed et al. [23] who recorded hypoperfusion in most of studies cases (90%).

Our results showed that the control group's ASL values ranged from 54.5 to 76, whereas the epilepsy group's values ranged from 39 to 68.5, with 49 serving as the cutoff, sensitivity 94.44% and specificity 91.67%. Consistent with the findings of Mingyuan et al. [21] who recorded cut off value of ASL was 46.76. Also, our results matched with the results of Gaxiola-Valdez, et al. [24] as in their study ASL was sensitive by 80% in localization of epileptic focus.

In agreement with our results about EEG finding, Xuan, et al. [25] EEG was normal in 22.7% of examined patients, while in the study of El-Kapany, et al. [20] EEG was negative in 68% of the studied patients.

The three modalities' diagnostic efficacy that were evaluated revealed that the highest AUC was for difference in NAA/Cho+ Cr (0.969), the showed sensitivity 94.44% and specificity 97.92%, while NAA/ Cr showed sensitivity 95.83% and specificity 77.08%, the AUC of the difference in rCBF was 0.917, with a cutoff value of ≤49, sensitivity 94.44%, and specificity 91.67%. While the changes in DTI parameters were examined, the difference in FA in the hippocampus exhibited an area under the curve (AUC) of 0.933, sensitivity of 86.11%, specificity of 97.92%, and a cutoff value of 0.196. Similarly, the difference in MD in the hippocampus exhibited an AUC of 0.851, with a cutoff value of 7.6, sensitivity 76.39%, and specificity 93.75%. In Consistency with our results, Reda, et al. [22] and El-Kapany et al. [20] reported that, MRS showed higher AUC than DTI with MRS AUC was 0.92 compared to 0.89 of DTI.

One of the study's limitations was the relatively small sample size. Lack of using higher modalities like PET MRI or post-operative assessment as a gold standard. No sufficient previous studies test the performance of combination of these three non-invasive MRI modalities in the diagnosis of MRI negative epilepsy as our study is considered to be one of the first studies to test combination of these three MRI modalities.

5. CONCLUSIONS

When assessing patients with epilepsy, MRI is an indispensable diagnostic tool. Nevertheless, a notable structural abnormality is not always apparent. Because of this, recent advances in the field of epilepsy have been made possible, allowing for the creation of new procedures and advanced imaging techniques in the field of epilepsy including MRS, DTI, and ASL. Non-invasive methods that can accurately identify the epileptogenic zone include MRS (which includes lower NAA/Cho+ Cr and NAA/Cr), DTI (which includes reduced FA and higher MD), and ASL (which takes hypoperfusion into account). Better diagnostic accuracy is achieved by combining MRS, DTI, and ASL than by using any one of these sequences alone. Also, the epileptogenic focus can be localized and lateralized with remarkable diagnostic accuracy using these methods. If this combination doesn't allowed in real life, MRS may have a solution that works extremely well. It is our firm belief that these MRI procedures should be routinely administered to patients presenting with non-lesional epilepsy.

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Conflict of Interest: None

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