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RESEARCH

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Usefulness of combined diffusion tensor imaging, arterial spin labelling and spectroscopic interictal analysis in refractory epilepsy

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Abstract

Background Epilepsy is a common neurological disorder especially in pediatric population. Patients with non-lesional epilepsy have normal conventional MRI findings. In the recent era of advances in neuroimaging studies, diffusion tensor imaging (DTI) and MR spectroscopy (MRS) can assess the tissue microstructure. Also, arterial spin labeling (ASL) is a noninvasive modality that evaluates cerebral blood flow. Multiple recent publications aimed at use of single or two new modalities in lateralization of epileptogenic focus in epilepsy, but the current study aimed to evaluate the added value of combined (DTI, ASL and MRS) in vivo localization of interactable epilepsy with negative conventional MRI findings.

Results This prospective case control study was carried out in the period from January 1st, 2022 to October 1st, 2022 after approval of local ethical committee in our institution. Written informed consent was obtained from patients and healthy volunteers who were enrolled in this study. The current study included 46 patients with temporal lobe epilepsy and 20 age- and sex-matched healthy volunteers as a control group. The mean age in the patient group was 22.3 ± 12.2 years, and in the control group, it was 23.8 ± 15.1 years. The highest area under the curve (AUC) was for spectroscopy (0.913), the difference in NAA/Cr showed sensitivity of 94.1% and a specificity of 90%, while NAA/Cho + Cr showed a sensitivity of 91.8% and a specificity of 88%, the difference in rCBF showed an AUC of 0.89, with a cutoff value of 3.815 had a sensitivity of 80.4% and a specificity of 85%. As regards DTI, the changes in DTI parameters show sensitivity of 79.6% and a specificity of 80% in lateralization of the epileptic focus. The difference in FA only showed an AUC of 0.86, with a cutoff value of 0.01 had a sensitivity of 77% and a specificity of 75% and the difference in MD only showed an AUC of 0.771, with a cutoff value of 0.545 had a sensitivity of 67.4% and a specificity of 70%. The diagnostic performance of MRS in terms of the AUC was significantly higher than ASL parameters (difference in NAA/Cr, $p = 0.033$ and difference in NAA/Cho + Cr, $p = 0.044$), and MD ($p = 0.02$). No other statistically significant differences were shown between the studied parameters. When the three methods were combined, all patients' epileptogenic foci were correctly localized and lateralized.

Conclusions Combining ASL, DTI and H-MRS provided excellent diagnostic performance in localization and lateralization of the epileptogenic focus. If this combination is not applicable in clinical practice, ASL could provide a considerably accurate and feasible method in this context. The present study supported the value of the new noninvasive MRI techniques in the elaboration of hidden brain pathology.

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Keywords Arterial spin labeling, Magnetic resonance spectroscopy, Diffusion tensor imaging, Focal epilepsy, Fractional anisotropy, Mean diffusivity, rCBF

Background

Epileptic activity is now explored in the light of new evidence on both brain organization and epileptogenic processes [1]. The combination of neuroimaging modalities in localization of epileptogenic focus has been developing in the last years [2]. According to the most recent International League Against Epilepsy classification, focal epilepsies include unifocal and multifocal disorders as well as seizures involving one hemisphere [3].

Epileptic patients must undergo brain conventional MRI to rule out structural abnormalities [4]. Malformations of cortical development as cortical dysplasia and hippocampal sclerosis are the most common focal brain pathologies in patients with MRI-negative epilepsy reported on surgical series [5]. Intracranial electroencephalography (iEEG) is now considered among the reference standard procedures for localizing epileptogenic focus and potentially planning surgical resection [6].

However, the role of advanced neuroimaging in localizing epileptogenic foci is expanding and developing with recent MRI machines and invention of new MR sequences [7]. ASL is a noninvasive MRI perfusion method that allows the assessment of regional cerebral blood flow by magnetically labeling protons from the inflowing blood as an endogenous diffusible tracer [8]. ASL does not require injection exogenous contrast agent or use of ionizing radiation to measure regional cerebral blood flow (rCBF) [9].

Moreover, proton MRS is a noninvasive method that quantitatively measures the regional metabolic changes and ratios that can precisely lateralize epileptogenic zone as well as assess either the epilepsy is controlled or not by presence of high lipids and lactate peaks [10]. DTI is a novel MR technique that is sensitive to the changes of structural integrity of the brain by quantitative assessment of fractional anisotropy, mean diffusivity and ADC values within the regions of interest [11].

The aim of this study was to investigate the capability of combined use of ASL, multi-voxel MRS and DTI in vivo identification of epileptogenic zone in patients with non-lesional focal epilepsy, by evaluation of the interictal changes in neurological metabolites, ratios by MRS, structural integrity changes by DTI and altered decreased rCBF in the irritative focus at the interictal period, compared to healthy individuals.

Methods

This prospective case control study was carried out in the period from January 1st, 2022 to October 1st, 2022 after approval of local ethical committee in our institution. Written informed consent was obtained from patients and healthy volunteers who were enrolled in this study. A total of 46 epileptic patients were referred from the Neurology Department to the Radiodiagnosis Department in our institution, with control group of healthy individuals ($N=20$) of nearly similar ages. Full neurological examination and EEG were performed in neurology department. The authors were blinded to subject's identity, age and epileptic focus site as determined by EEG recordings.

Inclusion criteria

All patients with interactable epilepsy in their interictal period (> 24 h free of seizures) were included in this study, who did not have any history of neurological disorders (as stroke, motor weakness, coma) and had no abnormal conventional MR findings.

Exclusion criteria

Patients with epilepsy caused by organic lesions as tumors, vascular lesions were excluded from the study, as well as claustrophobic patients and patients with MR non-compatible metallic devices, cardiac pacemakers and cochlear implants.

All cases and volunteers underwent MRI at 1.5 Tesla MRI unit. The patient removed metal pins, entered the machine with headfirst in supine position, foam padding to minimize head motion, using standard 16-channel head coil. The MRI protocol was as follows: slice thickness was 4 mm, the matrix was 256×256, and the field of view was 220–240 mm. Magnetic resonance imaging protocol included: axial T1WI (TR/TE = 300–600/10–30 m/sec), axial T2WI (TR/TE = 700–2000/80–100 m/sec), axial and/or coronal oblique FLAIR images (TR/TE/Inversion time (TI) = 6000–8000/140/1400), diffusion-weighted imaging (B value; 0, 1000), susceptibility-weighted imaging. MRS was acquired with 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. Post-processing was performed using MRI workstation software (ADW 4.7 Vantage, GE Medical Systems), MRS spectra datasets were analyzed qualitatively, as well as quantitatively to quantify NAA/

Choline + Cr, NAA/Choline, NAA/Cr, lipids/lactate peaks in short TE in both hippocampi. All metabolic ratios were tabulated as mean, standard deviation and ranges.

Continuous arterial spin labeling (CASL) perfusion imaging sequence that was implemented using 2.25 μT RF (corresponding to a 90° pulse of 2.6 ms duration and 1.6 mT/m gradient). By applying an amplitude modulated version of the labeling pulse using a sinusoidal modulation function, blood was alternately tagged and untagged. The total duration of the labeling/control pulses was 2 s. A gradient EPI sequence was used for image acquisition, with a post-labeling delay time of 1200 ms acquisition parameters were: field of view (FOV) = 25 cm, 64 × 64 matrix, TR = 4000 ms, flip angle = 90°, slice thickness 2 mm, inter-slice space 1 mm. For full k-space imaging, TE was 17 ms and each image acquisition took 45 ms.

The perfusion-colored maps of rCBF were automatically generated. The obtained findings were analyzed qualitatively by visual analysis color scale of maps, ranging from red (highly perfused areas) to blue (hypo-perfused areas). The hypo-perfused area in temporal lobe lateralized the epileptogenic focus of affected lobe. Quantitative analysis of rCBF at regions of interest (ROI) in both hippocampi measured about $1 \times 1 \times 1$ cm^2 that were placed manually using workstation analysis package with dedicated neuroimaging software.

Diffusion tensor imaging: High-resolution 3D T1-weighted spoiled gradient echo pulse sequence was acquired; (TR/TE/TI, 9.7/4.6/400 ms, flip angle (θ) = 35°, 124 slices 0.8 mm thick,

208 × 170 matrix, field of view (FOV) 23 cm 260 contiguous sections, acquisition time min. The DTI sequence consisted of single-shot spin echo-planar sequence in 40 encoding directions with the following parameters: TR = 8,830 ms; TE = 80 ms; acquisition matrix = 112 × 110 mm; acquisition voxel = 2.00/2.03/2.00 mm; FOV: right–left = 224 mm, anteroposterior = 224 mm, feet–head = 120 mm; voxel size: right–left = 2 mm, anteroposterior = 2 mm, slice thickness = 2 mm, reconstruction voxel size = 1.75 mm, *b* value = 800 mm/s, and number of slices = 60.

Data processing and analysis: The DTIs were transferred to the workstation (advantage window 4.7, GE Medical Systems), where they were converted to color-coded map images, various DTI indices such as FA and MD were generated. Regions of interest (ROIs) were drawn within identifiable white matter regions, namely both hippocampi.

DTI values for each ROI were calculated and compared with the corresponding ROIs in the opposite hemisphere. Additionally, the direction and anatomy of the tracts are seen in the directionally encoded FA maps, where a specific color is assigned to tracts running in three orthogonal planes.

Color-coded DTI maps were analyzed, both subjectively by visual comparison and quantitatively by comparing the FA and MD values with the contralateral normal side. All data were reviewed and analyzed by two experienced neuroradiologists with 9, 10 years of experience in neuroradiology, the final decision was given by a third experienced consultant of neuroradiology who had 12 years of experience in advanced neuroimaging field who gave his opinion in controversy opinions.

Each patient took a different ID number, and all patient data were blinded.

Statistical analysis

The SPSS for Windows version 28.0 software package (SPSS Inc., Chicago, IL) was used for statistical data analysis.

Categorical variables were described by frequency and proportion and quantitative variables were described by using mean, SD and range. Quantitative data were compared by using the student t test. P value less than 0.05 represented a significant difference. ROC curve analysis was used to determine the optimum cutoff values and maximal area under curve (AUC) with evaluation of diagnostic accuracy, sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively) of CAS, DTI and MV 1H-MRS of brain in localization and lateralization of epileptogenic focus.

Results

This prospective case control study was carried out in the period from January 1st, 2022 to October 1st, 2022. The current study included 46 patients with temporal lobe epilepsy (TLE) and 20 age- and sex-matched healthy volunteers as a control group. The mean age in the patient group was 22.3 ± 12.2 years, and in the control group, it was 23.8 ± 15.1 years. Females constituted 56.6% of the patients' group (26 patients) and 60% of the control group (12 participants). The patient's age of the first epileptic attack ranged from 1.5 months to 18.3 years, with a mean of 8.5 ± 5.3 years. The mean disease duration was 19.77 ± 12.47 years. Twenty patients (43.5%) had right-sided epileptogenic focus in EEG, and the remaining 26 (56.5%) had left-sided focus. Fourteen patients (30.4%) had a positive family. The attack frequency was daily in 5 patients (10.9%), weekly in 13 patients (28.3%), monthly in 13 patients (28.3%) and sporadic in 15 patients (32.6%) as described in (Table 1).

Table 1 The sociodemographic data and clinical characteristics of the studied cases

		Patients group (*N* = 46)	Control group (*N* = 20)	Test	*p* value
Age (year)	Mean ± SD	22.3 ± 12.2	23.8 ± 15.1	0.44[a]	0.66
Sex	Female	26 (56.6%)	12 (60%)	0.07[b]	0.79
	Male	20 (43.4%)	8 (40%)		
Laterality on EEG	Right	20 (43.5%)			
	Left	26 (56.5%)			
Age of onset (years)	Mean ± SD	8.5 ± 5.3			
Disease duration (years)	Mean ± SD	19.77 ± 12.47			
Frequency	Daily	5 (10.9%)			
	Weekly	13 (28.3%)			
	Monthly	13 (28.3%)			
	Sporadic	15 (32.6%)			

[a] Independent *t* test

[b] Chi-square test

N number, % percentage, *SD* standard deviation

In the patients' group, the mean fractional anisotropy (FA) was 0.148 ± 0.009 in the ipsilateral hippocampus and 0.157 ± 0.008 in the contralateral hippocampus, with a mean difference of 0.9 ± 0.003. In the control group, the mean FA values were 0.427 ± 0.009 and 0.442 ± 0.44 on the two sides with a mean difference of 0.106 ± 0.004.

Regarding the mean diffusivity (MD), the mean was $8.8 \pm 0.75 \times 10^{-3}$ m^2/sec in the ipsilateral hippocampus and $7.67 \pm 0.78 \times 10^{-3}$ m^2/sec in the contralateral hippocampus, with a mean difference of 1.14 ± 0.94 m^2/sec. The mean values were $7.36 \pm 0.8 \times 10^{-3}$ m^2/sec and $7.08 \pm 0.85 \times 10^{-3}$ m^2/sec in both sides of the control group, with a mean difference of 0.28 ± 0.45 m^2/sec as mentioned in (Table 2).

Concerning arterial spin labeling (ASL), perfusion abnormalities were seen in 41 patients (89.1%) in terms of hypoperfusion, of whom 38 patients (82.6%) were accurately lateralized and localized. Two patients (4.35%) showed hypoperfusion on both sides, one patient (2.17%) showed ipsilateral scattered hypoperfused foci, and five patients showed no perfusion abnormality (10.87%). All patients in the control group showed normal perfusion maps, with sensitivity about 82.6% as noticed in (Table 3).

Table 4 shows the assessment of the rCBF that showed the mean values in epileptic patients were 62.17 ± 6.57 and 75.18 ± 5.33 ml/100 g/min in the ipsilateral and contralateral hippocampus, respectively, with a mean difference of 13.01 ± 6.15 ml/100 g/min. In the control group, the mean values were 80.05 ± 5.1 and 82.17 ± 4.78 ml/100 g/min in both sides, with a mean difference of 2.13 ± 2.12 ml/100 g/min, statistically

Table 2 The DTI parameters in the studied cases

FA		Patients group (*N* = 46)	Control group (*N* = 20)	Test	*p* value
Ipsilateral	Mean ± SD	0.148 ± 0.009	0.427 ± 0.009	4.05[a]	< 0.001*
Contralateral	Mean ± SD	0.157 ± 0.008	0.442 ± 0.44	1.18	0.24
Difference	Mean ± SD	0.9 ± 0.003	0.106 ± 0.004	7.95	< 0.001*
Test		7.32[a]	0.07[a]		
p value		< 0.001*	0.94		
*MD*10*$^{-3}$					
Ipsilateral	Mean ± SD	8.8 ± 0.75	7.36 ± 0.8	7.04[a]	< 0.001*
Contralateral	Mean ± SD	7.67 ± 0.78	7.08 ± 0.85	2.74	0.008
Difference	Mean ± SD	1.14 ± 0.94	0.28 ± 0.45	3.88	< 0.001*
Test		7.08[a]	1.07[a]		
p value		< 0.001*	0.29		

FA fractional anisotropy, *MD* mean diffusivity, *SD* standard deviation, *N*: number

[a] Independent t test

*Statistically significant

Table 3 The ASL visual diagnosis (color maps) of the studied participants

	Patients group (*N* = 46)	Control group (*N* = 20)
Ipsilateral hypoperfusion (well-localized and well-lateralized)	38 (82.6%)	–
False localized	1 (2.17%)	–
False lateralized	2 (4.35%)	–
Normal	5 (10.87%)	20 (100%)
Sensitivity	82.6%	
Specificity	100%	

N Number, % Percentage

significant difference were noted between both groups with p value < 0.001*

Concerning MRS assessment in the patients' group, it demonstrated that the mean values of NAA/Cr and NAA/Cho + Cr in the affected hippocampus were 1.14 ± 0.42 and 0.45 ± 0.19, respectively, and in the contralateral hippocampus were 2.02 ± 0.54 and 1.16 ± 0.28, respectively, with mean differences of 0.88 ± 0.52 and 0.71 ± 0.33, respectively. In the control group, the NAA/Cr mean values on both sides were 2.28 ± 0.87 and 2.66 ± 0.8, with a mean difference of 0.38 ± 0.24, and the NAA/Cho + Cr mean values were 1.5 ± 0.36 and 1.7 ± 0.39, with a mean difference of 0.21 ± 0.26, statistically significant differences were detected at both NAA/Cr and NAA/Cho + Cr ratios between both diseased and control groups, p values were less than 0.001*, as described in (Table 5).

Assessment of the diagnostic performance of the three used modalities revealed that the highest area under the curve (AUC) was for spectroscopy (0.913), the difference in NAA/Cr showed sensitivity of 94.1% and a specificity of 90%, while NAA/Cho + Cr showed a sensitivity of 91.8% and a specificity of 88%, the difference in rCBF showed an AUC of 0.89, with a cutoff value of 3.815 had a sensitivity of 80.4% and a specificity of 85%. As regards DTI, the changes in DTI parameters show sensitivity of 79.6% and a specificity of 80% in lateralization of the epileptic focus. The difference in FA only showed an AUC of 0.86, with a cutoff value of 0.01 had a sensitivity of 77% and a specificity of 75% and the difference in MD only showed an AUC of 0.771, with a cutoff value of 0.545 had a sensitivity of 67.4% and a specificity of 70%. The diagnostic performance of MRS in terms of the AUC was significantly higher than ASL parameters (difference in NAA/Cr, $p = 0.033$ and difference in NAA/Cho + Cr, $p = 0.044$), and MD ($p = 0.02$). No other statistically significant differences were shown between the studied parameters. When the three methods were combined, all patients' epileptogenic foci were correctly localized and lateralized, as mentioned in (Table 6).

Table 5 The MRS parameters and ratios in the studied cases

		Patients group (*N* = 46)	Control group (*N* = 20)	Test	*p* value
NAA/Cr					
Ipsilateral	Mean ± SD	1.14 ± 0.42	2.28 ± 0.87	7.24[a]	< 0.001*
Contralateral	Mean ± SD	2.02 ± 0.54	2.66 ± 0.8	3.18[a]	< 0.001*
Difference	Mean ± SD	0.88 ± 0.52	0.38 ± 0.24	4.16[a]	< 0.001*
Test		8.72[a]	1.44[a]		
p value		< 0.001*	0.16		
NAA/Cho + Cr					
Ipsilateral	Mean ± SD	0.45 ± 0.19	1.5 ± 0.36	10.92[a]	< 0.001*
Contralateral	Mean ± SD	1.16 ± 0.28	1.7 ± 0.39	6.42[a]	< 0.001*
Difference	Mean ± SD	0.71 ± 0.33	0.21 ± 0.26	2.45	0.017*
Test		8.22[a]	1.69[a]		
p value		< 0.001*	0.1		

N Number, % percentage, *SD* Standard deviation, *NAA* N-acetylcysteine, *Cho* choline, *Cr* creatine

[a] Independent *t* test

*Statistically significant

Table 4 The rCBF measurements in the studied participants

rCBF (ml/100 g/min)		Patients group (*N* = 46)	Control group (*N* = 20)	Test	*p* value
Ipsilateral	Mean ± SD	62.17 ± 6.57	80.05 ± 5.1	4.77[a]	< 0.001*
Contralateral	Mean ± SD	75.18 ± 5.33	82.17 ± 4.78	0.73	0.47
Difference	Mean ± SD	13.01 ± 6.15	2.13 ± 2.12	4.86	< 0.001*
Test		7.22[a]	1.36[a]		
p value		< 0.001*	0.18		

rCBF Regional cerebral blood flow, *g* gram, *SD* Standard deviation, *N* Number

[a] Independent *t* test

p value* means statistically significant difference

Table 6 The differences of paired-sample area under the ROC Curves

Test result pair(s)	Test difference		AUC difference	95% confidence interval	
	z	*p* value		Lower bound	Upper bound
ASL diagnosis versus rCBF difference	0.447	0.66	0.003	− 0.001	0.004
ASL diagnosis versus MD difference	2.32	0.02*	0.007	0.001	0.007
FA difference versus rCBF difference	− 0.15	0.88	− 0.011	− 0.153	0.131
MD difference versus rCBF difference	1.7	0.09	0.119	− 0.019	0.257
FA difference versus NAA/Cr difference	1.446	0.148	0.105	− 0.037	0.247
FA difference versus NAA/Cho + Cr difference	1.625	0.104	0.143	− 0.029	0.315
FA difference versus ASL diagnosis	− 0.207	0.836	− 0.012	− 0.125	0.101
rCBF difference versus NAA/Cr difference	1.454	0.146	0.094	− 0.033	0.221
rCBF difference versus NAA/Cho + Cr difference	1.438	0.150	0.132	− 0.048	0.312
MD difference versus NAA/Cr difference	− 0.387	0.699	− 0.025	− 0.152	0.102
MD difference versus NAA/Cho + Cr difference	0.142	0.887	0.013	− 0.167	0.193
FA difference versus MD difference	1.785	0.074	0.130	− 0.013	0.273
NAA/Cr difference versus NAA/Cho + Cr difference	0.425	0.671	0.038	− 0.137	0.213
NAA/Cr difference versus ASL diagnosis	− 2.131	0.033*	− 0.117	− 0.224	− 0.009
NAA/Cho + Cr difference versus ASL diagnosis	− 2.019	0.044*	− 0.155	− 0.305	− 0.005

NAA N-acetylcysteine, *Cho* choline, *Cr* creatine, *FA* Fractional anisotropy, *MD* Mean diffusivity, *rCBF* Regional cerebral blood flow, *ASL* Arterial spin labeling

*Statistically significant difference

Discussion

Precise determination of the epileptogenic focus is crucial for proper patient assessment, treatment strategy and follow-up [6]. Electroencephalography (EEG) is commonly used for localization of the epileptogenic focus, however, with a limited diagnostic accuracy [7]. The advances in imaging technology that have been currently evolved allow the identification of brain parenchyma abnormalities via various modalities [8]. Despite that conventional MRI is still the workhorse for demonstration of the brain pathological lesions, about 30% of patients with complex localized seizures have normal brain MRI. Otherwise, the biochemical and biophysical alteration related to epileptic seizures could be exhibited in advanced functional MRI imaging techniques including proton MR spectroscopy (H-MRS), arterial spin labeling (ASL) and diffusion tensor imaging (DTI) [9]. In the present study, the role of H-MRS, ASL and DTI in the diagnosis of mesial temporal sclerosis when the conventional MRI is not conclusive [10].

This study showed that DTI in terms of FA and MD could serve as a localizing and lateralizing method during the assessment of the epileptogenic focus since significantly lower FA values and higher MD values were found in the ipsilateral hippocampus, with significantly higher differences between both sides shown in patients compared to controls. The current study findings are congruent with the study of Amr O et al. [6] who found that FA was a predictor of the epileptogenic focus in temporal lobe epilepsy. The value of FA in the focus localization is likely attributed to that DTI gives insight into the brain microstructural integrity that is mirrored in the FA as a measure of water diffusion. In addition, Alizadeh et al. [5] reported higher MD values in the ipsilateral hippocampus in patients with temporal lobe epilepsy. This higher value seems to be caused by the sclerosis and loss of tissue integrity that occur in the pathologically implicated hippocampus [7].

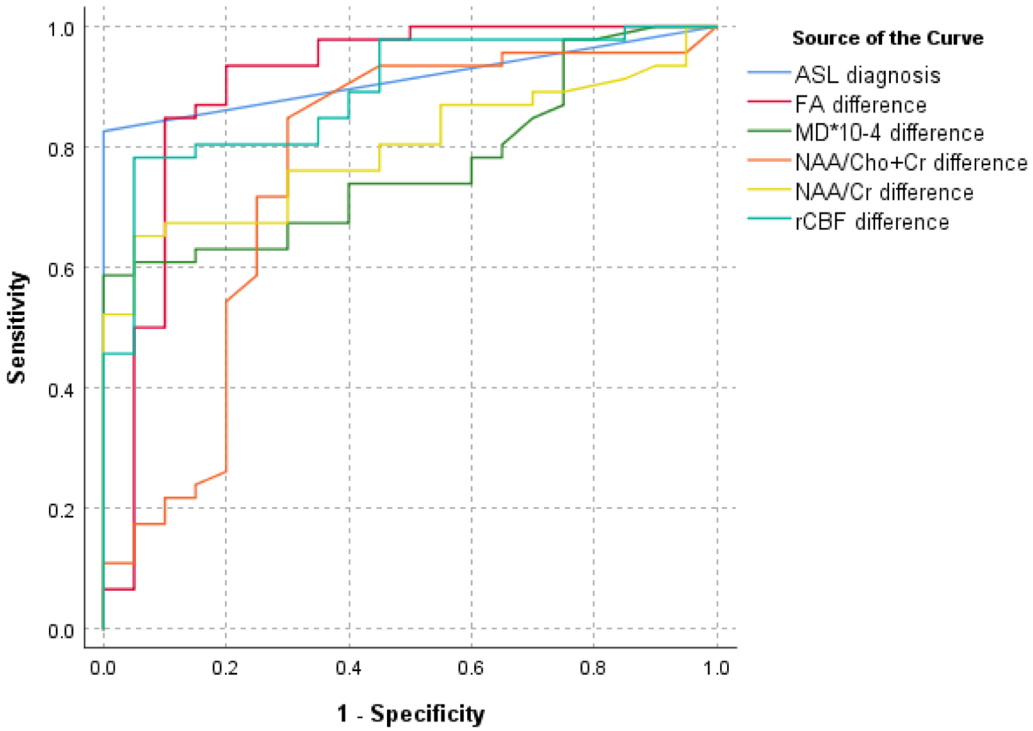
ASL is a noninvasive non-contrast perfusion-based MRI technique [8]. The present study showed that ASL mapping yielded a tool for lateralization and localization of the epileptogenic focus with fair sensitivity (80.4%) and specificity (85%). In accordance with previous studies [3, 9], the epileptogenic focus was apparent as a region of altered perfusion, which was hypoperfusion in all cases of the current study. Similarly, Mohamed et al. [10] reported hypoperfusion in ASL visual mapping with reduced rCBF in more than 90% of cases with temporal lobe epilepsy. The underlying pathophysiologic mechanisms of this altered perfusion were not fully elucidated. However, the plausible explanations were gliosis, cortical atrophy, neuronal destruction and/or decreased synaptic density within the epileptogenic focus [11].

The present study investigated H-MRS as a diagnostic method aiding in the localization and lateralization of the epileptogenic focus. Assessing the difference in

NAA/Cr and NAA/Cho + Cr showed a significant difference between patients and controls as well as between the epileptogenic focus and the contralateral side in the patients. These two parameters were chosen, since NAA is the most important spectrum in MRS as its decrease, markedly reflect the neuronal loss and dysfunction. Synthesis of NAA occurs in the neuronal mitochondria from acetyl-CoA and aspartate. Choline is also a marker for the integrity of the cell membrane. Creatine is needed for energy storage and transfer. It tends to have a relatively constant level and is mostly utilized as an internal standard for ratio calculations [12, 13].

The disturbed MRS spectra found in this study denote the neuronal destructive process that occurs in the epileptogenic focus. These findings go consistent with the previous studies that reported the benefits of MRS in the identification of epileptogenic focus [14, 15]. It is worth noting that our findings were contradictory to other studies. Davis et al. [16] reported that NAA/Cr was higher in the epileptogenic focus than in the contralateral area. Other studies showed comparable values on the two sides [17]. This was shown also in NAA/Cho + Cr [18]. This discrepancy could be due to variations in the disease features in the studied patients, time of assessment or the study design.

The current work showed that the lateralization and localization of the epileptogenic focus were best recognized by MRS followed by ASL, then DTI and the best is by combination of the three modalities for highest sensitivity and specificity. Combining the three modalities yielded precise localization and lateralization of all patients' epileptogenic foci (Figs. 1, 2, 3, 4, 5).



ASL: Arterial spin labelling

FA: Fractional anisotropy

MD: Mean diffusivity

NAA: N-Acetyl cystine, Cho: choline, Cr: Creatine

rCBF: Regional cerebral blood flow

Fig. 1 ROC analysis for the diagnostic performance of ASL, rCBF, FA, MD, NAA/Cr and NA/Cho + Cr differences in the localization and lateralization of the epileptogenic focus. ASL: Arterial spin labeling. FA: Fractional anisotropy. MD: Mean diffusivity. NAA: N-Acetylcysteine, Cho: choline, Cr: creatine. rCBF: Regional cerebral blood flow

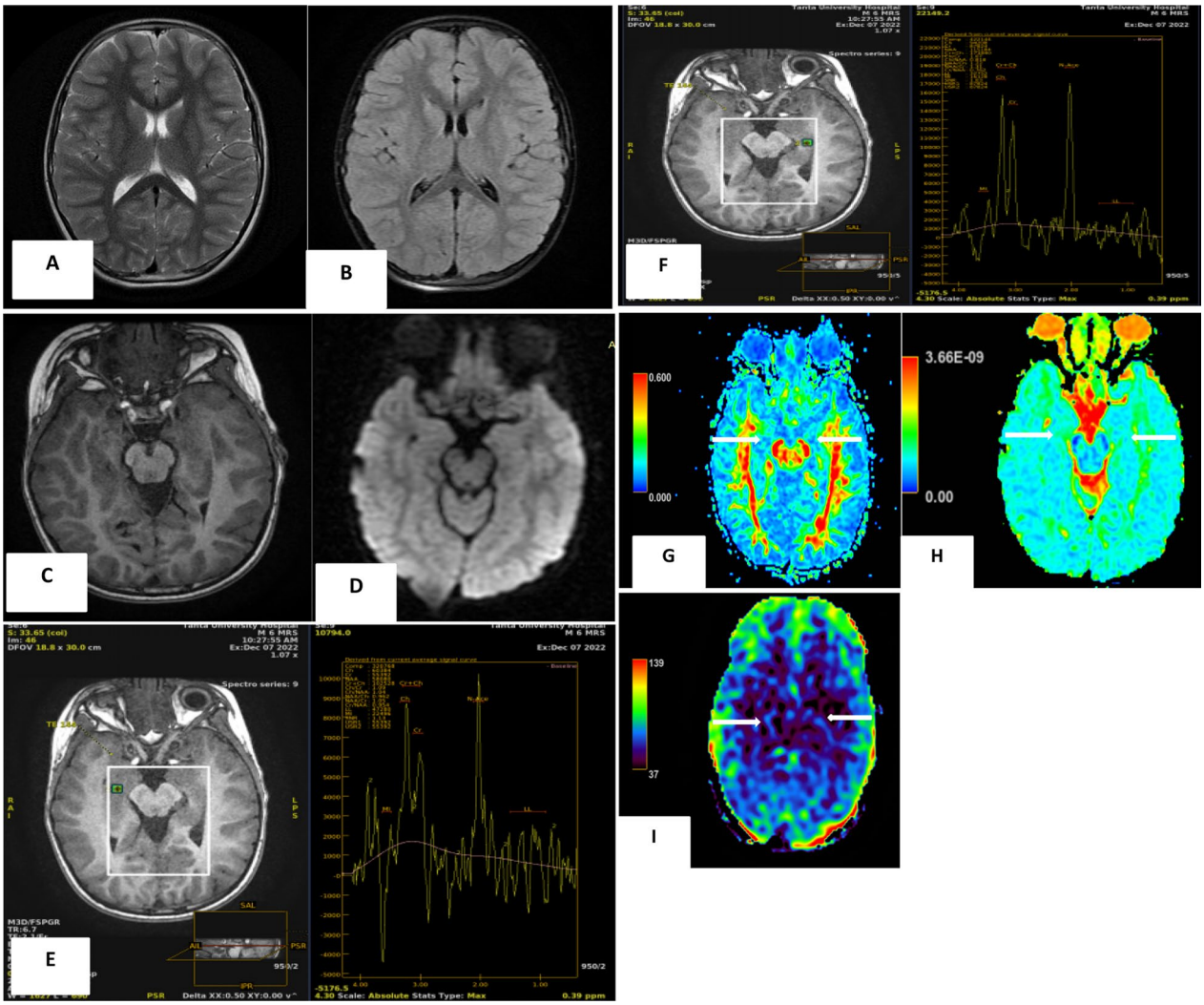


Fig. 2 A 11-year-old male patient presented with focal seizures. The structural MR images, including axial T2WI (**a**), axial FLAIR image (**b**), axial 3D T1WI (**c**), axial DWI (**d**), all are unremarkable and negative. The MV 1H-MRS picture maps are demonstrated in **e** and **f**. The MRS spectra 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 0.56 and 1, respectively, and on the left temporal lobe (**f**) measuring about 0.57 and 1.5, respectively. The FA map (**g**) revealed focal decrease in the FA value in both temporal lobes measuring 0.15 on the right side and 0.14 on the left side, respectively (white arrows), while MD map (**h**) revealed focal increase in the MD value in both temporal lobes measuring 8.6×10^{-3} m^2/sec on the right side and 8.8×10^{-3} $m.^2$/sec on the left side (white arrows). The ASL-MRI color-coded cerebral perfusion map (**i**) reveals scattered foci of hypoperfusion of both temporal lobes with rCBF measuring about 62 ml/100 g/min on the right side, while measuring 65 ml/100 g/min on the left side (white arrows)

Limitations of the study

We acknowledge that this work was limited by the small sample size. However, our study is the first to test the performance of combination of these three noninvasive MRI modalities in the diagnosis of temporal lobe epilepsy when the conventional MRI is normal. Further large-scale studies assessing other types of epilepsy are recommended.

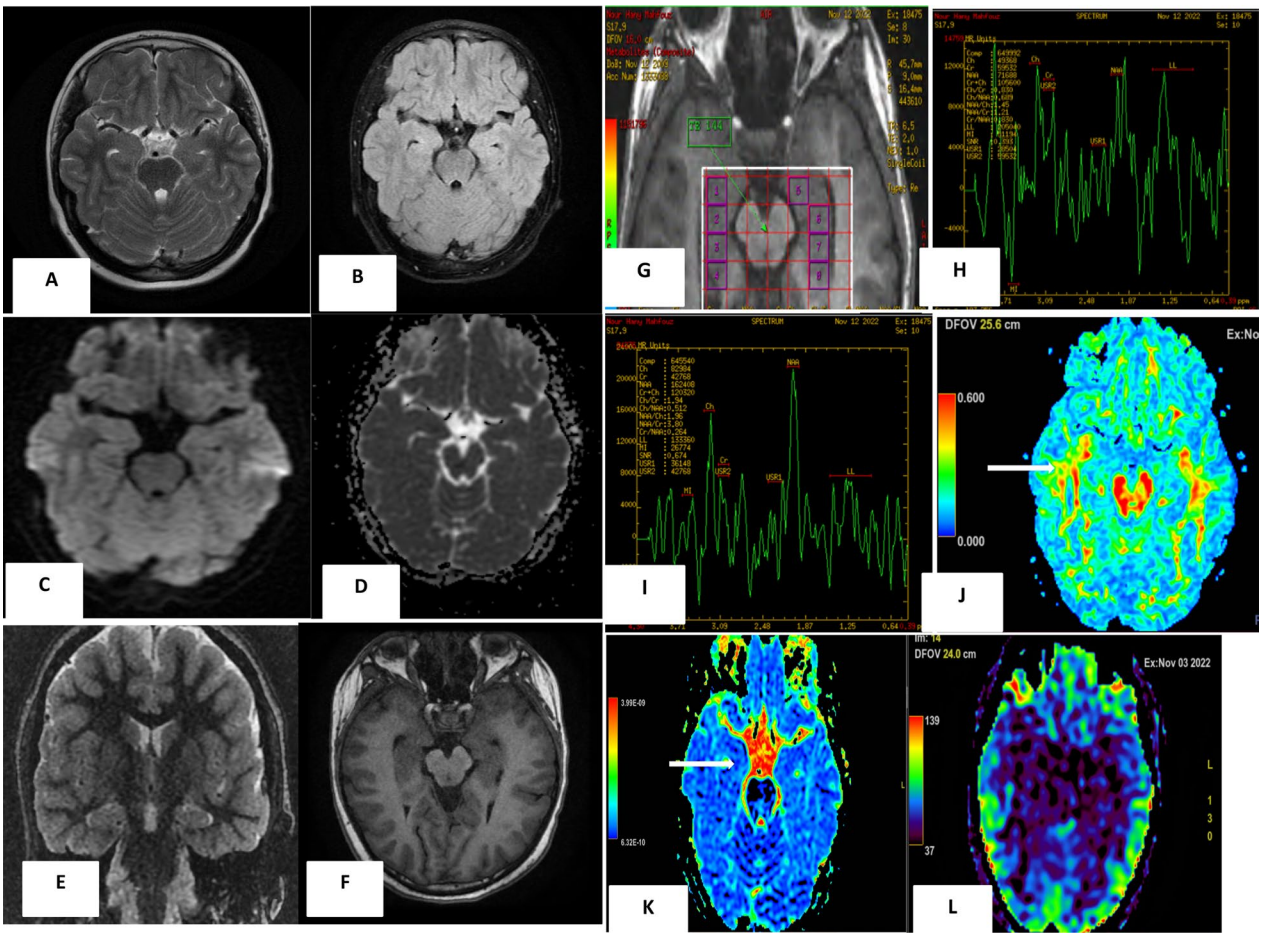


Fig. 3 A 17-year-old male patient presented with focal dyscognitive seizures. The structural MR images, including axial T2WI (**a**), axial FLAIR image (**b**) axial DWI (**c**) and ADC at b value 0 s/mm^2 (**d**) as well as coronal T2 IR and axial 3D T1WI (**e**) and (**f**), respectively), all are unremarkable and negative. The MV 1H-MRS picture maps are demonstrated in (**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 the right temporal lobe measuring about 0.6 and 0.8, respectively (**h**) in comparison with the contralateral non-epileptic left temporal lobe measuring about 1.3 and 3.8, respectively (**i**). The FA map (**j**) revealed focal decrease in the FA value in the right temporal lobe measuring 0.20 (white arrow), while MD map (**k**) revealed focal increase in the MD value in the right temporal lobe 8.4×10^{-3} m^2/sec (white arrow). The ASL-MRI color-coded cerebral perfusion map (**f**) reveals no perfusion abnormalities. The clinical examinations and EEG studies confirmed our results. (**l**) Enumeration letter of pictures in the case presentation

Conclusions

Combining ASL, DTI, and H-MRS provides excellent diagnostic performance in localization and lateralization of the epileptogenic focus. If this combination is not applicable in clinical practice, ASL could provide a considerably accurate and feasible method in this context. The present study supports the value of the new noninvasive MRI techniques in the elaboration of hidden brain pathology.

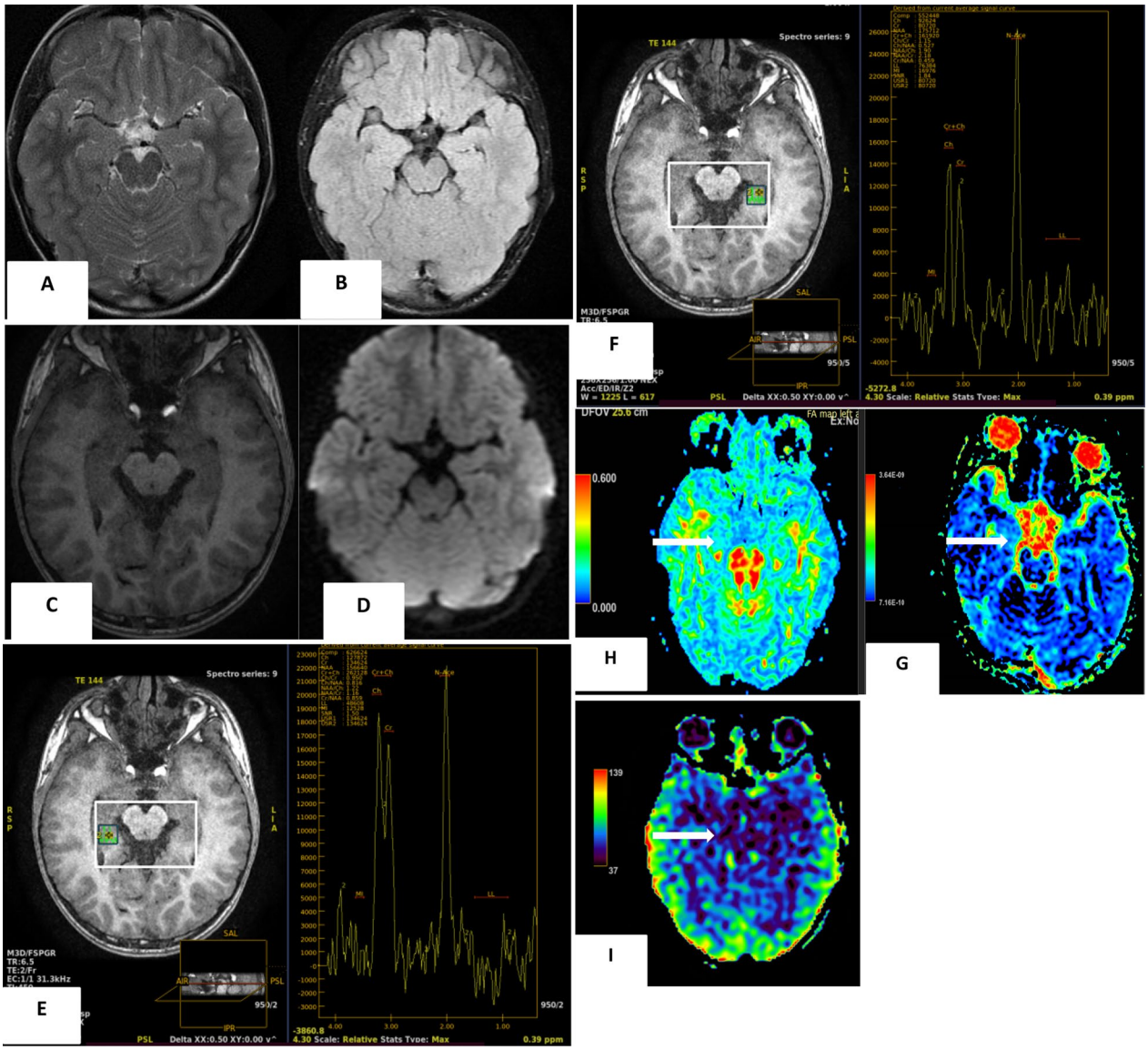


Fig. 4 A 33-year-old female patient, with focal impaired awareness seizures. The structural MR images: including axial T2WI (**a**), axial FLAIR image (**b**) and axial 3D T1WI (**c**), as well as axial DWI (**d**), all are unremarkable and negative. The MV 1H-MRS picture maps are demonstrated, the MRS 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 the right temporal lobe measuring about 0.59 and 1.1, respectively (**e**) in comparison with the contralateral non-epileptic left temporal lobe measuring about 1 and 2.1, respectively (**f**). The FA map (**g**) revealed focal decrease in the FA value in the right temporal lobe (white arrow) measuring 0.18, while MD map (**h**) reveals focal increase in the MD value in the right temporal lobe measuring 8.6×10^{-3} m^2/sec (white arrow). The ASL-MRI color-coded cerebral perfusion map (**i**) reveals scattered foci of hypoperfusion of the right temporal lobe with rCBF measuring about 72 ml/100 g/min (white arrow). The clinical examinations and EEG studies confirmed our results

Recommendations

- Continued data collection in a larger sample, longer duration with the ability of multi-points time of assessment is highly recommended to validate these observations with a larger scale on different types of epilepsy.
- Multi-centric research studies in different MRI machines of higher Tesla are recommended in the future research field.

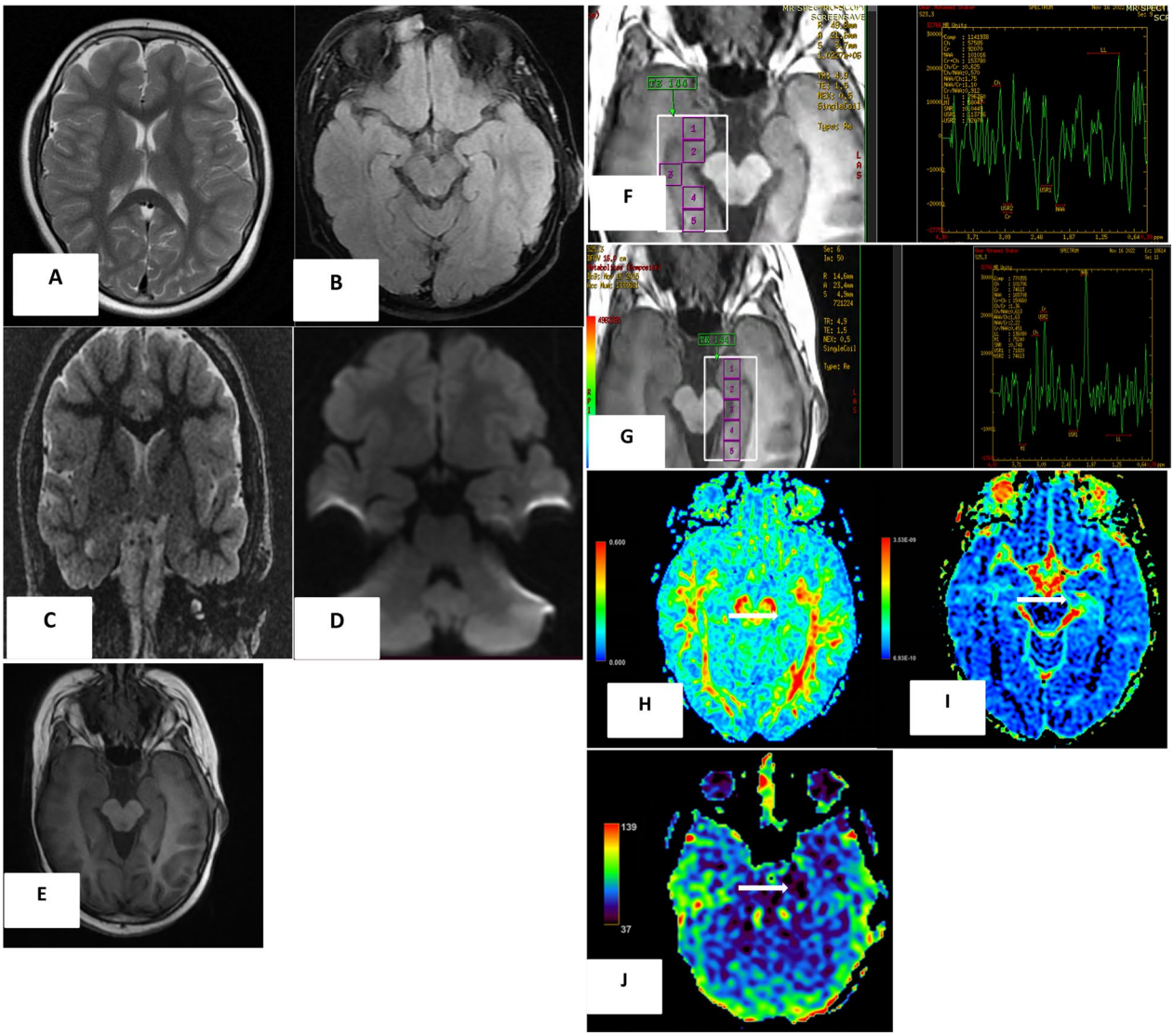


Fig. 5 A 14-year-old male patient, with focal epilepsy. The structural MR images, including axial T2WI (**a**), axial FLAIR image (**b**) coronal T2 IR (**c**), axial DWI (**d**), as well as axial 3D T1 (**e**), all are unremarkable and negative. The MV 1H-MRS picture maps demonstrate, the MRS spectra 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 the left temporal lobe measuring 0.6 and 1.1, respectively (**f**) in comparison with the contralateral non-epileptic right temporal lobe measuring 1 and 2.2, respectively (**g**). The FA map (**h**) revealed focal decrease in the FA value in the left temporal lobe measuring 0.22 (white arrow), while MD map (**i**) reveals focal increase in the MD value in the left temporal lobe measuring 8.8 × 10–3 m^2/sec (white arrow). The ASL-MRI color-coded cerebral perfusion map (**i**) reveals a focal hypoperfusion of the left temporal lobe with rCBF measuring about 69 ml/100 g/min (white arrow). The clinical examinations and EEG studies confirmed our results

Abbreviations

MRI	Magnetic resonance imaging
FLAIR	Fluid-attenuated inversion recovery
MRS	Magnetic resonance spectroscopy
NAA	N-Acetyl aspartate
Cr	Creatine
Cho	Choline
ml	Myo-inositol
Glx	Glutamine and glutamat
Lac	Lactate
SD	Standard deviation
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
MD	Mean diffusivity
ASL	Arterial spin labelling
rCBF	Regional cerebral blood flow

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Author contributions
AR suggested the research idea, ensured the original figures and data in the work, minimized the obstacles to the team of work, correlated the study concept and design and had the major role in analysis, AE supervised the study with significant contribution to design the methodology, manuscript revision and preparation, also correlated the clinical data of patient and matched it with the findings, drafted and revised the work. SE collected data in all stages of manuscript and performed data analysis. All authors read and approved the manuscript and ensure that this is the case.

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Availability of data and materials
The authors confirm that all data supporting the finding of the study are available within the article and the raw data supporting the findings were generated and available at the corresponding author on request.

Declarations

Ethics approval and consent to participate
Informed written consents were taken from the patients and healthy volunteers, the study was approved by ethical committee of Tanta University hospital, faculty of medicine (2021–5–28).

Consent for publication
All participants included in the research gave written consent to publish the data included in the study. Authors accepted to publish the paper.

Competing interests
The authors declare that they have no competing of interests.

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References

1. Baumgartner C, Koren JP, Britto-Arias M, Zoche L, Pirker S (2019) Presurgical epilepsy evaluation and epilepsy surgery. F1000Research 8:1818. https://doi.org/10.12688/f1000research.17714.1
2. Tamilia E, Madsen JR, Grant PE, Pearl PL, Papadelis C (2017) Current and emerging potential of magnetoencephalography in the detection and localization of high-frequency oscillations in epilepsy. Front Neurol 8(14):1–8
3. Zhang J, Zhang H, Li Y, Yuan M, Zhang J, Luo H et al (2021) Arterial spin labeling for presurgical localization of refractory frontal lobe epilepsy in children. Eur J Med Res 26(1):88
4. John S, Karin T (2022) Advanced neuroimaging techniques in epilepsy. Curr Opinion Neurol 35(2):189–195
5. Alizadeh M, Kozlowski L, Muller L, Ashraf N, Shahrampour S, Mohamed F et al (2019) Hemispheric regional based analysis of diffusion tensor imaging and diffusion tensor tractography in patients with temporal lobe epilepsy and correlation with patient outcomes. Sci Rep 9(215):1–8
6. Amr O et al (2018) Role of diffusion tensor imaging in detection and lateralization of temporal lobe epilepsy. Med J Cairo Univ 86(9):2501–2505
7. Bansal V, Kumar S, Sharma S, Sharma S, Sood RG (2017) Usefulness of pulsed arterial spin labeling magnetic resonance imaging in new-onset seizure patients and its comparison with dynamic susceptibility contrast magnetic resonance imaging. J Neurosci Rural Pract 8(4):569–574
8. Kim BS, Lee ST, Yun TJ, Lee SK, Paeng JC, Jun J et al (2016) Capability of arterial spin labeling MR imaging in localizing seizure focus in clinical seizure activity. Eur J Radiol 85(7):1295–1303
9. Lee SM, Kwon S, Lee YJ (2019) Diagnostic usefulness of arterial spin labeling in MR negative children with new onset seizures. Seizure 1(65):151–158
10. el Mohamed RE et al (2020) Arterial spin-labelling and magnetic resonance spectroscopy as imaging biomarkers for detection of epileptogenic zone in non-lesional focal impaired awareness epilepsy. Egypt J Radiol Nucl Med 51(1):200
11. Goodman AM, Szaflarski JP (2021) Recent advances in neuroimaging of epilepsy. Neurotherapeutics 18:811–826. https://doi.org/10.1007/s13311-021-01049-y
12. Tan Q, Sun H, Wang W, Wu X, Hao N, Su X et al (2018) Quantitative MR spectroscopy reveals metabolic changes in the dorsolateral prefrontal cortex of patients with temporal lobe epilepsy. Eur Radiol 28(11):4496–4503
13. Aun AAK, Mostafa AA, Aboul Fotouh AM, Karam KS, Salem AA, Salem A et al (2016) Role of magnetic resonance spectroscopy (MRS) in non lesional temporal lobe epilepsy. Egypt J Radiol Nucl Med 47(1):217–231
14. Daichi S (2021) Making the invisible visible: advanced neuroimaging techniques in focal epilepsy. Front Neurosci Sec Brain Imaging Methods. https://doi.org/10.3389/fnins.2021.699176
15. Emad A, Medhat R, Medhat E, Sameh A (2019) Advanced MR imaging techniques in the diagnosis of epilepsy. Benha Med J. https://doi.org/10.21608/bmfj.2020.14508.1012
16. Davis KA, Nanga RP, Das S, Chen SH, Hadar PN, Pollard JR et al (2015) Glutamate imaging (GluCEST) lateralizes epileptic foci in non-lesional temporal lobe epilepsy. Sci Transl Med. 7(309):309ra161
17. Bandopadhyay R, Singh T, Ghoneim MM, Alshehri S, Angelopoulou E, Paudel YN, Piperi C, Ahmad J, Alhakamy NA, Alfaleh MA, Mishra A (2021) Recent Developments in diagnosis of epilepsy: scope of MicroRNA and technological advancements. Biology 10(11):1097. https://doi.org/10.3390/biology10111097
18. Ercan K, Gunbey HP, Bilir E, Zan E, Arslan H (2016) Comparative lateralizing ability of multimodality MRI in temporal lobe epilepsy. Dis Markers. https://doi.org/10.1155/2016/5923243

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