Original Article

Role of Interictal Arterial Spin Labeling Magnetic Resonance Perfusion in Mesial Temporal Lobe Epilepsy

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Abstract

Context: Electrophysiological and hemodynamic data can be integrated to accurately identify the generators of abnormal electrical activity in drug-resistant focal epilepsy. Arterial Spin Labeling (ASL), a magnetic resonance imaging (MRI) technique for quantitative noninvasive measurement of cerebral blood flow (CBF), can provide a direct measure of variations in cerebral perfusion associated with the epileptogenic zone. **Aims**: 1. To evaluate usefulness of ASL for detecting interictal temporal hypoperfusion to localize the epileptogenic zone in patients of drug resistant mesial temporal lobe epilepsy (MTLE). 2. Correlation of localization of epileptogenic zone on ASL MR perfusion with structural MRI and EEG. **Methods and Materials**: 30 patients with MTLE and10 age and gender matched normal controls were studied. All patients underwent ictal video EEG monitoring non-invasively, MR imaging with epilepsy protocol and pseudocontinuous ASL (PCASL) perfusion study. Relative CBF (rCBF) values in bilateral mesial temporal lobes were measured utilizing quantitative analysis of perfusion images. A perfusion asymmetry index (AI) was calculated for each region. **Results**: In patients, ipsilateral mesial temporal rCBF was significantly decreased compared with contralateral mesial temporal rCBF ($p = 0.021$). Mesial temporal blood flow was more asymmetric in patients than in normal control participants ($p = 0.000$). Clear perfusion asymmetry on PCASL-MRI was identified despite normal structural-MRI in 5 cases, agreeing with EEG laterality. **Conclusions**: Pseudo-continuous ASL offers a promising approach to detect interictal hypoperfusion in TLE and as a clinical alternative to SPECT and PET due to non-invasiveness and easy accessibility. Incorporation of ASL into routine pre-surgical evaluation protocols can help to localize epileptogenic zone in surgical candidates.

Keywords: Arterial spin labelling, cerebral blood flow, interictal, magnetic resonance imaging perfusion, mesial temporal lobe epilepsy.

Introduction

Cerebral Blood Flow (CBF) reflects the amount of blood perfusion in the brain, often defined as ml of blood per 100 gram of brain per minute. Many pathological conditions are associated with abnormal CBF values, including acute stroke, brain tumour, neurodegenerative diseases and epilepsy. 30 to 40% of patients with epilepsy have drug resistant seizures. Mesial temporal lobe epilepsy (MTLE)[1,2] is the most common type of drug resistant epilepsy in adults. Thus, it is important to establish a robust method suitable for longitudinal and cross-sectional studies of drug resistant MTLE non-invasively.

ASL is a non-invasive MR perfusion technique to quantify CBF at tissue level. This study was undertaken to evaluate usefulness of ASL for detecting CBF alterations related to the epileptogenic zone i.e., interictal temporal hypoperfusion in order to localize the epileptogenic zone in surgical candidates of MTLE. Correlation of localization of epileptogenic zone on ASL MR perfusion with structural MRI and EEG was also evaluated.

Mesial temporal sclerosis accounts for the majority of patients undergoing anteromedial temporal lobectomy for drug resistant TLE and surgery is successful in reducing or eliminating seizures in 70-90% of patients.[3-5] Therefore, precise preoperative localization of the epileptogenic zone is crucial to spare non-epileptogenic brain tissue as best as possible and minimize postoperative neurological deficits.[5]

Presurgical workup for MTLE includes EEG, structural MRI and cerebral perfusion measurement techniques like PET, SPECT, CT Perfusion, DSC-MRI, ASL-MRI.

Structural MRI[6-9] markers of MTS are found in 60-70% of patients with TLE. True coronal IR or 3D SPGR sequences show a shrunken hippocampus and widening of the adjacent temporal horn and/or choroid fissure.[10] Abnormal T2/FLAIR hyperintensity with obscuration of the internal hippocampal architecture is typical. Associated alterations like atrophy of ipsilateral temporal lobe, atrophy of the ipsilateral fornix and mammillary body can be demonstrated in severe and long-standing cases.

On FDG PET, temporal lobe hypometabolism is the typical finding. Ictal SPECT shows hyper-perfusion in the

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epileptogenic zone during seizure activity; hypoperfusion in the interictal period is common.[9] MR perfusion demonstrates similar changes to SPECT with blood perfusion depending on when the scan is obtained. During the peri-ictal phases, perfusion is increased, not only in the mesial temporal lobe but often in large parts of temporal lobe and hemisphere. In interictal periods, conversely, perfusion is reduced.

PET,[11,12] SPECT,[13,14] dipole localization or electrical source imaging (ESI),[15,16] and EEG-functional MRI (fMRI)[17-19] can all offer localization information. However, PET and SPECT have poor temporal and spatial resolution, are invasive and require radiation exposure as compared to functional MRI and EEG which have excellent temporal and spatial resolution, are non-invasive and have no radiation exposure.

ASL MRI[20] has been applied to noninvasively study and quantify perfusion changes related to the epileptogenic zone without the need for contrast agents. The advantages of ASL MRI over [18F] FDG-PET or SPECT[21-23] are that it has no radiation exposure, has better spatial and temporal resolution, it is non-invasive and requires no injection, and thus it is easily repeatable and reproducible as clinically indicated and favourable for pediatric patients.

Even in patients with normal structural MRI, ASL can detect perfusion asymmetries and interictal ipsilateral hypoperfusion, thus it can identify the process in its early stages i.e., before hippocampal volume loss, thereby helping to resolve difficulties in lateralisation of epileptogenic zone.

Subjects and Methods

Patient population

This study was undertaken in the department of Radio diagnosis, Dayanand Medical College and Hospital, Ludhiana, conducted between January 2018 to December 2018. It was a prospective study. 30 patients (age range 10-72 years, mean age 34.2 years; 18 females, 12 males) of drug resistant mesial temporal lobe epilepsy in whom ictal EEG telemetry has unequivocally shown unilateral mesial temporal seizure onset and were referred for MRI to the department of radiodiagnosis were included in the study.

All patients were evaluated during the interictal phase with latest seizure episode at least 72 hours prior to brain perfusion imaging. The study also included 10 age and gender matched normal controls (age range 21-68 years, mean age 47.4 years; 6 females, 4 males). Patients with evidence of structural lesions on MRI (except mesial temporal sclerosis) were excluded. A detailed relevant history about seizure onset, duration, frequency, type of seizure and antiepileptic drugs (AEDs) was evaluated. All patients received ictal scalp video-electroencephalography (EEG) monitoring non-invasively to localize the epileptogenic zones with recording of at least 2- 8 ictal events. Informed consent was obtained from each subject. The study was approved by the institutional ethics committee.

Magnetic resonance imaging acquisition

MRI scans were performed on patients and controls, using a SIEMENS MAGNETOM SKYRA 3 Tesla MR scanner with a 20 CHANNEL head coil. PCASL perfusion image was obtained with PQ2T sequence. It was performed with adequate background suppression and pulse labelling plane placed just below the volume of interest using these acquisition parameters: Label duration = 700 ms, post labelling delay or inversion time = 1990 ms, TR = 4600 ms, TE = 16.2 ms, frequency = 123.15, NEX (number of excitations) = 1, number of slices = 40, FOV (field of view) = 210, slice thickness = 3 mm, bandwidth = 2695. Epilepsy protocol was performed which included T2 axial, FLAIR axial, T1 axial, T2 coronal oblique, T1 IR coronal oblique, T2 sagittal, 3D T1 MPRAGE Volumetry, SWI and DWI for anatomical imaging.

Image processing and data analysis

Data post-processing was performed on SYNGOVIA workstation for 2D ASL with automated generation of relative CBF (rCBF) maps [Figures 1 and 2] from each subject. At least 3 regions of interest (ROIs) of 4–7 mm^2 were drawn over each manually defined region on structural T1 MRI scan which were copied to ASL images on the same anatomical level. Medial temporal ROIs included uncus, amygdala, hippocampus and para-hippocampus. Lateral temporal ROIs were taken in superior, middle and inferior temporal lobes. The ROI values of each region were then averaged to obtain

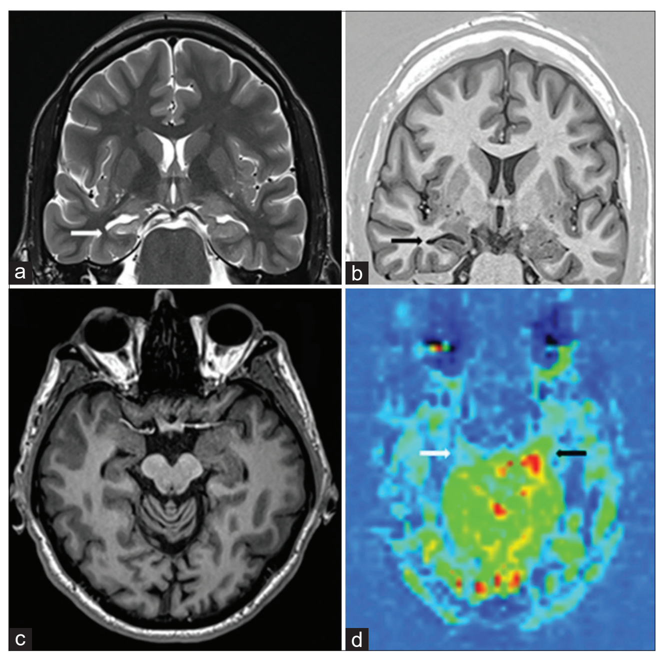

Figure 1: Structural and Perfusion MRI data acquired from a 51 year old male with right temporal lobe epilepsy. Coronal T2 weighted MR image (a) shows right hippocampal atrophy and hyperintensity with loss of digitations (white arrow). Coronal T1 IR image (b) and axial T1 MPRAGE image (c) show right hippocampal atrophy and dilatation of temporal horn of ipsilateral lateral ventricle. Axial PCASL MR image (d) shows decreased perfusion in right mesial temporal lobe (white arrow) as compared to that on left side (black arrow)

the mean rCBF value for each region. Using these values of each region, the average rCBF values for both mesial temporal lobes were calculated to identify the side of reduced rCBF. For patients, a perfusion asymmetry index (AI) was calculated from the mean rCBF values identified in each region, using the following formula: AI (%) = 100·(ipsilateral − contralateral)/[(ipsilateral + contralateral)/2]. A negative AI implies relative hypoperfusion in the affected temporal lobe. For controls, AI was calculated by the left-right asymmetry: AI (%) = 100·(left − right)/[(left + right)/2].

Statistical analysis

All statistical calculations were done using SPSS 21 (Statistical Package for the Social Science) version statistical program for Microsoft Windows. Data were described in terms of range; mean ± standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups was done using the Mann-Whitney U test. For comparing categorical data, Chi square (χ^2) test was performed and exact test was used when the expected frequency is less than 5. A probability value (*p* value) less than 0.05 was considered statistically significant.

Results

On PCASL MRI, mesial temporal rCBF was significantly decreased ipsilateral to the epileptogenic zone (p = 0.021) detected on EEG, as compared to the contralateral normal side in the interictal period. In cases, PCASL MRI derived mean rCBF ± SD was 334.9 ± 129.1 on the ipsilateral temporal side, and 427.8 ± 165.9 on the contralateral temporal side [Table 1]. There was no significant difference (p = 0.917) in mesial temporal rCBF values between both sides in control participants [Table 2]. In controls, PCASL derived mean mesial temporal rCBF ± SD was 389.70 ± 127 on the right side, and 383.6 ± 131.05 on the left side. There was no significant difference in lateral temporal relative CBF values bilaterally (*p* value 0.25) in patients.

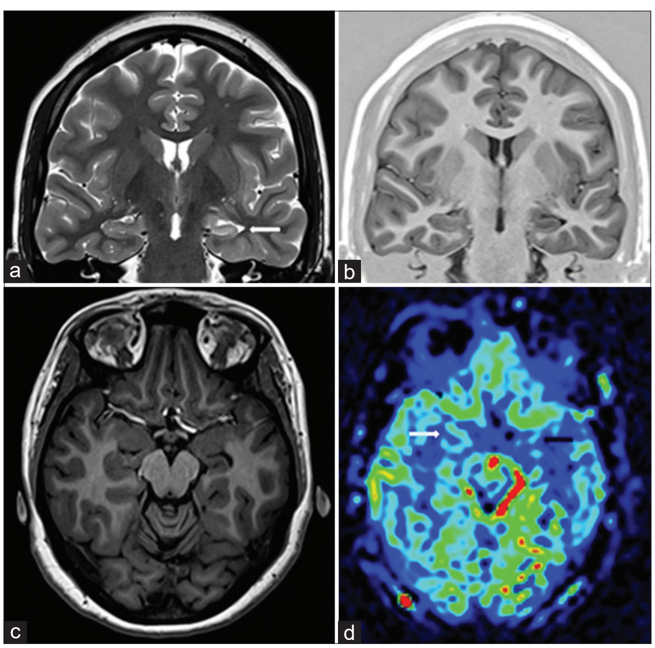

Figure 2: Structural and Perfusion MRI data acquired from a 24 year old female with left temporal lobe epilepsy. Coronal T2 weighted MR image (a) shows left hippocampal atrophy and hyperintensity with dilatation of temporal horn of ipsilateral lateral ventricle (white arrow). Coronal T1 IR MR image (b) and axial T1 MPRAGE image (c) show left hippocampal atrophy. Axial PCASL MR image (d) shows decreased perfusion in left mesial temporal lobe (black arrow) as compared to that on right side (white arrow)

PCASL MRI found mesial temporal perfusion asymmetries exceeding 1-SD of control mean value in all patients. The mean AI ± SD for the mesial temporal rCBF was 24.01 ± 16.75% in cases and 2.68 ± 14.79% in controls [Table 3]. Thus, the mesial temporal perfusion was more asymmetric in patients than in controls with a significant difference (p = 0.000) as shown in Figure 3.

In 5 patients (S No. 19, 20, 21, 22, 26) with epileptogenic zone lateralised on EEG, but structural MRI showing normal study, PCASL MRI detected interictal asymmetries in mesial temporal perfusion and mesial temporal hypoperfusion ipsilateral to EEG focus, thus localising the epileptogenic zone as shown in Table 4.

Table 1: Mean Mesial Temporal Blood Flows Measured with Pseudo-continuous ASL MRI in MTLE Patients

	Ipsilateral MTL		Contralateral MTL		*Z*	*P*
	Mean	SD	Mean	SD		
PCASL rCBF	334.92	129.16	427.87	165.99	-2.368	0.021

Table 2: Mean Mesial Temporal Blood Flows Measured with Pseudocontinuous ASL MRI in Controls

	Right MTL		Left MTL		*Z*	*P*
	Mean	SD	Mean	SD		
PCASL rCBF	389.70	127.00	383.62	131.05	0.105	0.917

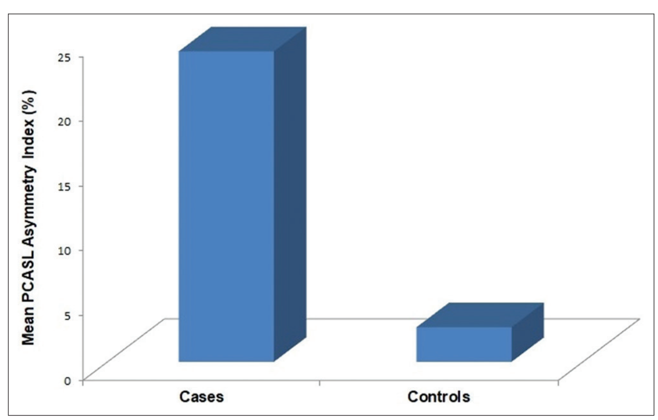

Figure 3: Comparison of Mean asymmetric indices of mesial temporal perfusion in patients and controls

The direction of the asymmetry with PCASL MRI was in agreement with EEG lateralization in each case except for patient nos. 8 and 24. This patient no. 8 had right temporal epileptogenic zone on EEG, but PCASL found left temporal hypoperfusion, with structural MRI showing left hippocampal sclerosis. In patient 24, EEG showed left temporal epileptogenic zone with left hippocampal sclerosis on structural MRI, however PCASL found interictal hypoperfusion in the right mesial temporal lobe, thus depicting PCASL-EEG discordance.

One patient S No. 9 with right MTS underwent right anteromedial temporal lobectomy, and is now seizure free.

Discussion

The main interest of ASL MR Perfusion study in the context of epilepsy is to locate a potential epileptogenic zone[20] in order to give better surgical outcomes in patients of drug resistant epilepsy. Vascular and perfusion alterations are indeed crucial steps in the etiopathogenesis of epilepsy. During the acute peri-ictal period, the CBF is typically increased due to pathologic neuronal activity, while in the chronic interictal period, CBF is typically reduced as the epileptogenic region typically is less functional and active compared with the normal brain tissue.

This study reports the role of MR perfusion in patients of mesial temporal lobe epilepsy in interictal period, measured by the pseudo-continuous ASL (PCASL) technique at 3T. The results of this study suggest that PCASL MRI is worthy of further study as a potential method for lateralization of epileptic foci by detecting interictal asymmetries in mesial temporal perfusion, particularly in patients with normal structural MRI.

Localisation of epileptogenic zone in MTLE patients with PCASL MRI perfusion

In the present study, ipsilateral mesial temporal rCBF was significantly decreased in patients with MTLE as compared to contralateral mesial temporal CBF (p = 0.021) in the interictal period, thus localising the epileptogenic zone. Our findings are consistent with CASL study by Wolf *et al.*[24] who also detected interictal mesial temporal lobe hypoperfusion on the side of epileptogenic zone in patients of MTLE, which had significant correlation with lateralisation based on FDG-PET hypometabolism, hippocampal volumes and clinical evaluation. In correspondence to this, PASL study by Lim YM *et al.*[25] also reported that ipsilateral mesial temporal CBF was lower than contralateral CBF with both PASL and PET techniques.

Table 3: Mean PCASL MRI Asymmetric Indices of Mesial Temporal Perfusion in Patients and Controls

	Cases		Control		Z	P
	Mean	SD	Mean	SD		
PCASL MRI asymmetry index (%)	24.01	16.75	2.68	14.79	4.481	0.000

Similarly, PASL study by Pendse N *et al.,*[26] found hypoperfusion in the affected temporal lobe in all cases with temporal lobe epilepsy on both interictal ASL and PET maps. PASL study by Storti *et al.,*[27] also demonstrated that epileptogenic zone in the interictal phase was associated with an area of hypoperfusion and hypometabolism. In the study by Galazzo *et al.*,[22] ASL detected interictal hypoperfusion at the site of the epileptogenic zone in 10/12 patients.

In our study, there was no significant difference (p - 0.917) in mesial temporal perfusion values between both sides in control participants. This is in correspondence to CASL study by Wolf *et al.*[24] and PASL study by Lim *et al.,*[25] who concluded the same result. Thus, mesial temporal blood flow was more asymmetric in patients of MTLE with mean asymmetry index i.e., AI ± SD of 24.01 ± 16.75% than in normal control participants with mean AI ± SD of 2.68 ± 14.79% by a significant difference (p = 0.000). Our findings are consistent with CASL study by Wolf *et al.,*[24] in which mean AI ± SD was 6.76 ± 4.28% in cases, and that in controls was 4.92 ± 2.76%. Similar results were reported in PASL study by Lim *et al.,*[25] in which mean AI ± SD was 18.16 ± 13.3% in cases, and that in controls was 11.02 ± 7.81%.

Role of PCASL MR Perfusion in localisation of epileptogenic zone in patients with normal structural MRI

Perfusion decrease in the affected mesial temporal lobe could result from mesial temporal atrophy. However in our study, clear perfusion asymmetry on PCASL MRI was identified despite normal structural MRI in 5 cases, lateralising to the same side as detected on EEG.[21-23] In concordance to this, perfusion asymmetry was detected by Wolf RL *et al.,*[24] in 1 case of normal anatomical MRI, and by Lim *et al.,*[25] in 3 cases showing normal anatomical MRI. These findings

Table 4: Role of PCASL MRI in Epileptogenic Zone Lateralisation in Patients with EEG- Structural MRI Discordance

Patient S. No.	EEG Epileptogenic Zone	Structural MRI	PCASL MRI Perfusion	
			Mesial Temporal rCBF	Asymmetry index (%)
20	Right temporal	Normal	Right hypoperfusion	-28.9
22	Right temporal	Normal	Right hypoperfusion	-24.1
26	Right temporal	Normal	Right hypoperfusion	-20.3
19	Left temporal	Normal	Left hypoperfusion	-26.5
21	Left temporal	Normal	Left hypoperfusion	-7.8
8	Right temporal	Left hippocampal sclerosis	Left hypoperfusion	28.9

suggest dissociation between structure and function. Thus, it is possible that functional alterations such as receptor loss, hypoperfusion, or hypometabolism may precede structural atrophy in the epileptic zone. The study done by Giovacchini G *et al.,*[28] showed that 5-HT1A receptors are reduced in mesial temporal lobe in patients with temporal lobe epilepsy and could be detected in mesial temporal regions in patients with normal MR scans. Because MR hippocampal volume measurements indicate a later stage in mesial temporal sclerosis, a functional technique such as perfusion MR imaging may be useful in identifying the process in its early stages (i.e., before volume loss) or in helping to resolve difficulties in lateralization.

PCASL MR Perfusion-EEG Correlation to localise epileptogenic zone

In this study, the direction of the asymmetry with PCASL MRI was in agreement with ictal video-EEG[15,16] lateralization in each case except for patient nos. 8 and 24. The patient no. 8 had right temporal epileptogenic zone on EEG, but ASL showed left temporal hypoperfusion with left hippocampal sclerosis on structural MRI. In patient no. 24 with left temporal epileptogenic zone on video-EEG, PCASL found right temporal hypoperfusion with structural MRI showing left hippocampal sclerosis, thus depicting ASL-EEG discordance. Similar to this, study by Lim YM *et al.,*[25] also showed PASL- ictal video-EEG non-agreement in one of the cases who had bitemporal seizure foci on EEG, but both PASL and PET showed left temporal hypoperfusion. Similarly, in the study by Wolf *et al.*,[24] one patient had discordant findings lateralising to the left side on CASL, whereas EEG and PET findings lateralised to the right.

The discordance between EEG and ASL might be possible due to the following reasons. Patients with severe hippocampal sclerosis may present contralateral temporal scalp ictal onset, which has been called “burned-out hippocampus”.[29] Severely injured hippocampi incapable of spreading ictal activity to the ipsilateral adjacent temporal neocortex, would spread, instead, to contralateral temporal/neocortex, visualized by scalp electrodes with false lateralization in scalp EEG. Mesial temporal lobe epilepsy (MTLE) is frequently associated with bilateral abnormalities, reflected by structural and functional neuroimaging, interictal EEG and neuropsychological alterations. In some cases, seizures seem to start almost simultaneously bilaterally in the mesio-temporal structures. Sometimes hippocampal seizures exhibit a so called “flip-flop” ictal pattern that is bilaterally alternating sequences of facilitated and suppressed trains of ictal discharges. This results in apparent gross discordance between imaging and scalp ictal recordings.

Compared to previous ASL and PET perfusion studies, pseudo-continuous ASL sequence used in this study offers as good or even better reliability in repeated measurements for both young and elderly subjects. It takes advantage of Continuous ASL‘s superior signal to noise ratio and Pulsed ASL‘s high labelling efficiency without the need for long labelling pulses.

Limitations

Caution needs to be exercised in the interpretation of our findings on account of certain limitations. Our institutional review board permitted imaging studies in only 10 controls to minimise inconvenience. This might have impacted our analysis. The number of subjects is small and larger studies might provide more precise results. Lastly, we were unable to undertake correlation of our findings with histopathology as all but one of the subjects could not proceed to surgery, including those with normal MRI.

Conclusion

In conclusion, our results demonstrated that PCASL MRI Perfusion study offers a non-invasive, inexpensive and repeatable method for lateralization of epileptogenic zone in MTLE patients, particularly in drug resistant ones, in order to provide better surgical outcomes and reduced post-operative deficits, making it a potential alternative to invasive examinations with PET and SPECT. Also, in patients with normal structural MRI, by detecting perfusion asymmetries and interictal ipsilateral hypoperfusion, ASL MR Perfusion study is useful in identifying the process in its early stages i.e., before hippocampal volume loss, thereby helping to resolve difficulties in lateralisation of epileptogenic zone.

Key Messages

1. In patients with MTLE, Pseudo-continuous ASL successfully detects significant decrease in ipsilateral mesial temporal CBF compared with contralateral side in the interictal period, hence localising the epileptogenic zone.
2. In patients with normal structural MRI, by detecting perfusion asymmetries and interictal ipsilateral hypoperfusion, ASL MR Perfusion study is useful in identifying the process in its early stages i.e., before hippocampal volume loss, thereby helping to resolve difficulties in lateralisation of epileptogenic zone.

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Conflicts of interest

There are no conflicts of interest.

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