

Hippocampal Profiling with Localised MR T2 Relaxometry for Hippocampal Sclerosis: Early Detection and Localisation

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Abstract

Background: Hippocampal sclerosis (HS) is the most common cause of Drug-resistant Temporal lobe epilepsy, radiologically characterized by atrophy and increased T2/FLAIR signal. Its accurate detection is important to guide surgery which is the best treatment option. Quantitative evaluation using MR volumetry and T2 relaxometry can yield higher sensitivity in early detection and localization of HS than visual analysis alone. We emphasize the role of T2 relaxometry in the evaluation of Hippocampal sclerosis in our study. The aims and objectives are to evaluate the role of T2 relaxometry in detection and localization of HS, to describe the advantages and accuracy of relaxometry over conventional MR imaging. **Subjects and Methods:** Prospective study of 2 years duration conducted on 30 patients of either sex and all age groups who presented with high electro-clinical suspicion of HS. MR imaging was done with standard epilepsy protocol on a 3T MRI. T2 relaxometry was done to assess T2 relaxation time of hippocampus using multi-echo sequence. **Results:** In our study, left MTS was found in 60% of the patients, right MTS was found in 33.3 % of the cases, and bilateral MTS was found in 6.7 % of the cases. Out of 30 patients, 90.0% (27 cases) showed positive findings and 10 % (3 cases) showed normal findings on MR visual analysis. Out of 27 cases with positive MR findings, 25 cases (92.59%) showed increased T2 relaxometry values and 2 cases (7.41%) showed normal T2 relaxometry values. All three cases with negative findings on MR visual analysis showed increased T2 relaxometry values. The T2 relaxometry values were raised on side of epileptogenic origin and mean values were 126.16 ± 6.49 ms in right MTS and 124.01 ± 11.71 ms in left MTS cases. Overall, T2 relaxometry exhibited a sensitivity of 90%, specificity of 93.3 percent, positive predictive value (PPV) of 93.1 percent, negative predictive value (NPV) of 90.32 percent, and diagnostic accuracy of 91.6 percent. **Conclusion:** T2 relaxation times were elevated in 93.3% of hippocampal sclerosis cases showing its high sensitivity in evaluation of HS. The conclusion is Hippocampal evaluation with T2 relaxometry has significant role in early detection and localization of HS.

Keywords: Hippocampal sclerosis, MRI, T2 relaxometry.

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Introduction

The most common aetiology of medically refractory temporal lobe epilepsy (TLE) cases is hippocampal sclerosis (HS) which is characterized by Gliosis and neuronal cell death.^[1] In hippocampal sclerosis, more than half of the neurons are lost, most notably pyramidal cells in regions CA1, CA2, and CA4, as well as granular cells later in the dentate gyrus.

Patients are usually young adults with or without prior insult in childhood. They present with characteristic aura, minor or major events like behavioural arrest, staring looks, automatisms and secondary generalised tonic-clonic seizures etc.

Presurgical examination aims for accurate localization and lateralization of the seizure foci as detecting a specific problem early in a disease process will result in a better

surgical outcome. This involves phase I [Non-invasive modalities like video-EEG, MEG, MRI, interictal PET, ictal SPECT and neuropsychological examination] and phase II evaluation [invasive procedures such as subdural grid/strip placement and/or depth electrode placement for electrocorticography (ECoG) and stereo-electroencephalography are used (SEEG)].

Although surgery is the treatment of choice to achieve seizure free status, invasive examinations may be avoided if an abnormality can be detected non-invasively on magnetic resonance imaging (MRI) that correlates well with other clinical findings like semiology, EEG and neuropsychological testing.^[2]

Hippocampal atrophy, loss of internal hippocampal architecture, and T1-hypointensity and T2-hyperintensity are typical MRI findings in HS.^[3] However, Qualitative or Visual analysis alone may be insufficient to detect HS early in the disease process. Here comes the role of quantitative

imaging techniques like localised hippocampal volumetry and T2 relaxometry in the early detection and localisation of HS.^[4,5,6]

Quantitative volumetry of the hippocampus can be used to assess volume loss (atrophy), a sign of neuronal cell death which may be difficult to appreciate visually in the brain.^[7,8]

T2 relaxometry is a technique for measuring T2 relaxation time, which is a tissue intrinsic feature. It can detect modest disease and aid in the lateralization of temporal lobe epilepsy, even in the absence of hippocampal atrophy which is the most common finding in HS. And thus, T2 relaxometry helps in the early detection of seizure focus and better surgical outcome.^[5,6]

We emphasize the role of T2 relaxometry in the evaluation of Hippocampal sclerosis in our study.

Imaging features of MTS

1. Qualitative analysis- Conventional MRI: T1, T2, FLAIR - Primary signs: i) Hippocampal atrophy, ii) T2/FLAIR hyperintensity of the hippocampus, iii) Loss of internal architecture and normal digitations of the hippocampus head. Secondary signs: i) Dilatation of the adjacent temporal horn, ii) Atrophy of the mamillary body, fornix (circuit of papez) and amygdala, iii) T2 hyperintensity in the white matter of anterior temporal lobe with loss of grey-white differentiation in the ipsilateral anterior temporal lobe, iv) Atrophy of the collateral white matter bundle.
2. Quantitative analysis: i) Hippocampal volumetry: Decreased hippocampal volume, ii) T2 relaxometry: Increased T2 relaxation time.
3. Functional analysis- i) PET: Hypometabolism in the temporal lobe, ii) Ictal SPECT: Hyper perfusion of seizure focus, iii) MR spectroscopy: Reduced N-acetyl-aspartate (NAA), Reduced NAA to creatine or NAA to (choline + creatine) ratios iv) Diffusion-Weighted Imaging: Sclerotic hippocampi may show abnormally elevated ADCs, even when conventional MRI is normal, likely reflecting early change, v) Diffusion Tensor Imaging: DTI has shown reduced fractional anisotropy and increased mean diffusivity, vi) Fiber Tract tractography: Diffusion tensor fiber tracking of major white matter tracts is especially helpful in planning surgery, vii) Functional MRI: to locate eloquent regions of the brain that should be preserved when planning lesional resective surgery.

T2 Relaxometry

T2 relaxometry is a method for determining the T2 signal alterations associated with hippocampal sclerosis. T2 relaxation times, unlike T2 signal changes, are absolute quantities that can be objectively compared to control values.

T2 signal is a biomarker of early epileptogenic degeneration to some extent. There is a correlation between hydration alterations in hippocampus and epileptogenicity development. The T2 signal increase in the hippocampus was mainly affected by gliosis in dentate gyrus, where a high proportion of glial cells show abnormal activity. The advantage of T2 relaxometry is shown especially when it is used in the evaluation of early MTS or those with no

atrophic changes which often escape visual detection. It is also helpful in diagnosis of bilateral MTS cases. In addition, the method of quantitative measurement provides a more sensitive and objective mean in determination of related diseases.

Spin echo sequences acquired at multiple echo durations are commonly used to measure T2 relaxation times, with the time constant of the exponential signal decay indicating the rate of T2 relaxation. Dual echo time investigations have been proven to be quickly obtained, provide consistent T2 values, and be beneficial in the assessment of both the hippocampus and other cerebral structures, despite the fact that reported techniques have employed anywhere from 2 to 16 echo times.^[9]

Long multi echo acquisitions, such as the Carr-Purcell-Meiboom-Gill sequence, were used to create T2 maps at first.^[5] A dual spin echo sequence, on the other hand, can dependably provide quick whole brain coverage, with T2 values computed by fitting a mono-exponential to the two values.^[10,11,12]

Manual delineation of circular/elliptical zones of interest (ROIs) is the current clinical technique to measure T2 values in hippocampus. This is time-consuming, and there may also be challenges in properly positioning a region of interest while preventing contamination by cerebrospinal fluid (CSF).^[10,12]

T2 relaxometry physics^[13,14]

Relaxometry, or the measurement of relaxation rates, is based on physical features of nuclei relaxing to the ground state after being stimulated by an RF pulse. This relaxation is caused by fluctuations in the strength of the local magnetic field that occur at random. T2 relaxation occurs immediately after the RF pulse and is caused by the dephasing of individual magnetic moments of protons.

Because protons receive a slightly different magnetic field and revolve at a slightly different frequency, they fall out of phase. This transverse relaxation happens due to magnetic field inhomogeneities induced by the magnet or magnetic particles present in the tissues, as well as movement of molecules within the tissue. Relaxometry is the measurement of the T1, T2 or T2* relaxation time in each voxel of an image. These relaxation times have been offered as techniques of monitoring the status of brain tissue throughout time.

Spin-echo or gradient echo sequences can be applied to generate relaxometry maps. Rather than T2, is assessed in the gradient echo sequence. Because of the higher magnetic field inhomogeneities, the resulting images have a lower resolution. At least two pictures are required to construct a map of relaxation rate ($R2=1/T2$) or relaxation time (T1 or T2) utilizing spin echo sequences. The sensitivity of this technique is determined by the sequence, time of repetition (TR), duration of echo (TE), number of pictures obtained with varied TE, and model used to match the experimental data.

For T2 weighted pictures, the selected TE values should be closer to the tissue's T2 value when employing a single spin echo capture. If TE is substantially longer than T2, the relaxed part of signal intensity versus TE will be weighted in the fit. Relaxometry employs a multi-spin-echo sequence

in general (MSE). In this situation, if the first echo was significantly shorter than the tissue's T2 value, a larger number of echoes will be needed to assess high T2 values. Because of the high repetition rate, thermal factors will contribute to the spins' dephasing, making T2 even shorter. However, if the first TE is long, the interval between shots will only allow a few images from the TE range to be captured in order to calculate T2. Using a single spin-echo sequence (SSE) and repeating the acquisition for distinct echoes is one way to overcome an MSE's incompatibility. Unfortunately, this strategy will necessitate significantly longer scan times. If T2 values are very short, short TE values will also be required. As a result, a single spin echo session might be employed to improve the precision of the relaxometry technique for assessing tissue iron overload. In relaxometry evaluation, increasing TR also enhances the signal-to-noise ratio (SNR).

TR is usually at least three times that of T1. Increased TR, on the contrary, increases acquisition time. The value and quantity of TEs are also crucial factors in relaxometry. The SNR improves as the number of TEs increases. The TE values should be picked from a range that is near to the sample's T2 values. T2 measurements will be more accurate if the value is closer to TE but sufficiently longer than T2 variations in the tissue's region of interest (ROI).^[15]

Aim and Objectives of the Study

1. To evaluate the role of T2 relaxometry in detection and localization of HS
2. To describe the advantages and accuracy of relaxometry over conventional MR imaging.

Subjects and Methods

Our study is a Prospective study done over a period of 24 months in a sample of 30 patients of all age groups and either sex who were referred to Radiology department from general medicine, neurology, and neurosurgery with high electro clinical suspicion of temporal lobe epilepsy.

Inclusion Criteria

- Patients with high clinical suspicion of TLE.
- Patients with fronto-temporal spikes and sharp waves on EEG.

Exclusion Criteria

- Patient having history of claustrophobia.
- Patient having history of metallic implants insertion, cardiac pacemakers and metallic foreign body in situ.
- Patients with evidence of structural brain lesions on MRI other than hippocampal sclerosis.

Data Collection

A detailed history with various patient's data which includes patient demographic details, hospital ID, and study reports are collected and entered in a specially designed Proforma.

Protocol for MRI Brain (Epilepsy Protocol) Patient Positioning

- Position : Supine

- Orientation : Head first
- Coil : Head matrix coil
- Head was positioned in the head matrix coil, patient immobilized with pads & velcro bands. Centred the laser beam localizer over the glabella.

Imaging Sequences

- Localiser
- 3D CUBE FLAIR
- T2 – WI AXIAL, SAGITTAL
- DWI, ADC
- FSPFGR
- CORONAL INVERSION RECOVERY
- T2 - spin echo - coronal – multi echo sequence – Relaxometry

Image Planning of T2 Relaxometry Sequence

A three-plane localizer was taken in the beginning to localise, and the other sequences planned.

Coronal oblique for CORONAL- T2 - 4mm / T2 relaxometry sequence

- Coronal high-resolution slices planned on sagittal plane
- The position block plane is perpendicular to the hippocampus's long axis.
- The positioning block in the other two planes were checked
- An appropriate angle given perpendicular to the midline of the brain
- The whole temporal lobe covered with sufficient Slices.

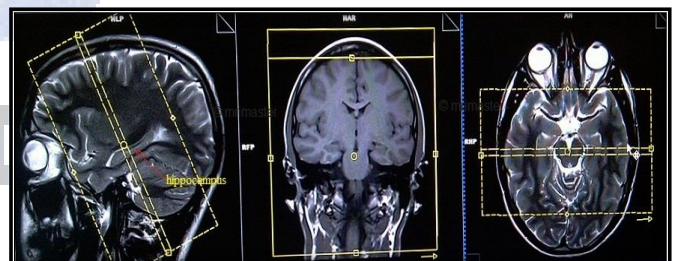


Figure 1: Planning of coronal oblique (T2 Relaxometry sequence) in sagittal, coronal, and axial plane.

T2 relaxometry protocol & post processing

Table 1: Protocol for T2 relaxometry

Parameters	
Scan plane	Oblique coronal
Mode	2D
Pulse sequence family	Spin echo
Pulse sequence	FSE-T2
TR (ms)	2000
TE (ms)	Multiple echoes ranging from 10 -100 ms
FOV (mm)	240
Phase FOV (mm)	190
Slice thickness (mm)	4
Spacing (mm)	1
Matrix	192 x 256
NEX	1
Scan time	5 min 12 sec

Analysis Software

The T2 maps were created by fitting a single exponential to the signal intensity data from corresponding pixels from all

eight echoes using a computer software. The T2 relaxation time for each pixel was then determined, and an image was created in which the pixel intensity matched the calculated T2 relaxation time. The mean hippocampal T2 relaxation time was calculated by manually marking a region of interest (ROI) in the largest possible circular area within the anterior, middle, and posterior sections of the hippocampus, corresponding to the three sections of the hippocampus designated as hippocampal head, hippocampal body, and hippocampal tail, respectively, while avoiding boundaries where partial volume effects with CSF might arise. Mean of the three values were calculated. When T2 values were outside the normal range and more than two standard deviations outside the typical hippocampus T2 relaxation durations, they were termed abnormal. In our study T2 relaxometry value of > 113 ms were considered abnormal.

Regions of Interest

Measurement of T2 relaxation time was achieved by placing a circular region of interest (< 20 sq mm) over a predefined area of anatomy, as described previously for hippocampal regions of interest. All measurements were obtained bilaterally by using anatomic landmarks.

Data Analysis

T2 relaxometry values of the bilateral hippocampus for all the 30 patients were collected and analysed. Then a table with graphical representation was done showing T2 Relaxometry values of bilateral hippocampi in patients who came with high clinical suspicion of MTS.

Results & Discussion

A total of thirty patients with high electroclinical suspicion of mesial temporal sclerosis were included in the present study and followed up during our study period. The results are as follows.

In our study, mean age of the participants in our study is 28.93 ± 10.46 years. Majority of study participants (66.6%) belonged to the age group of 21-40 years, 23.3% belonged to 8-20 years, 3.3% belonged to 41-50 years, 6.7% belonged to 51-60 years. 36.7% were male and 63.3% were female.

Mean age of onset of seizures is 14.83 ± 6.83 years. Majority of patients (46.7%) were in age group of 11-20 years, 33.3% of patients were in the age group of 3-10 years and 20% were in the age group of 21-31 years.

The antecedent events to seizures were observed to be none in 43.3% of the study participants, 23.3% had febrile seizures, 16.7% had family history of seizures, 6.7% had perinatal insult, 6.7% had encephalitis, 3.3% had seizure during 2nd pregnancy.

Laterality of mesial temporal sclerosis

In our study, left MTS was found in 60% of the patients, right MTS was found in 33.3 percent of the cases, and bilateral MTS was found in 6.7 percent of the cases.

In the study conducted by Coan AC et al,^[16] showed 62 left MTS, 54 right MTS, 6 bilateral MTS with left-sided predominance, 3 bilateral MTS with right-sided predominance. The findings made in this study showed a slight predominant laterality towards left and this finding

made was in consonance with the present study.

In the study done by Falip p et al,^[17] 34% had right MTS, 60% had left MTS and 4.3% had bilateral MTS. This finding was in consonance with the present study.

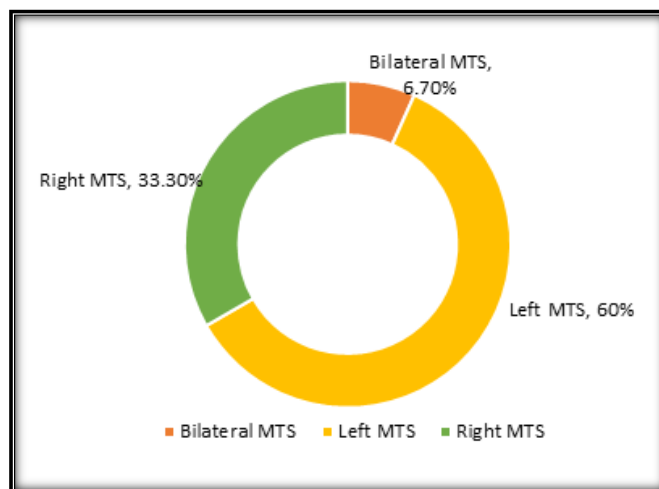


Figure 2: Pie diagram showing laterality of MTS

MR Visual analysis

In our study, 63.3% had a normal finding on MR visual analysis in right hippocampus, 33.3% had volume loss with T2 FLAIR hyper intensity and 3.3% had volume loss.

In MR visual analysis of left hippocampi, 40% of the patients showed normal findings, 43.3% had volume loss with T2 FLAIR hyper intensity, 13.3% had FLAIR hyper intensity with no volume loss, 3.3% had volume loss.

T2 relaxometry

In our study T2 relaxometry in right hippocampi, 60% of the cases showed normal T2 relaxometry values and 40% of the cases showed increased T2 relaxometry values. The mean T2 relaxometry values in cases of right MTS was 126.16 ± 6.49 ms.

In T2 relaxometry of left hippocampus, in 60% of the cases had increased and 40% it had normal values. The and mean T2 relaxometry value in cases of left MTS was 124.01 ± 11.71 ms.

In two bilateral MTS cases of our study, T2 relaxometry were increased in both hippocampus

The mean T2 relaxometry values were more on epileptogenic side compared to contralateral side. There was significant difference in the mean values of T2 relaxometry on both sides.

In the study conducted by Chen Hui et al,^[18] they have observed that the mean T2 relaxometry values were significantly higher in epileptogenic side as compared with contra-lateral regions of patients with normal structure and this finding was in consonance with the present study. They have also observed that quantitative measurements of T2 relaxation time have rendered it a more powerful discriminating parameter and it is seemingly more suitable than volumetry in lateralization and localization in cases of early and subtle MTS showing a more stable performance

In the study conducted by Bernasconi et al,^[6] showed that the epileptogenic zone in all (100%) patients with MR-

positive MTLE and 82% of patients with MR- negative MTLE could be depicted by T2 relaxometry

Diagnostic accuracy of T2 relaxometry

In comparison to conventional analysis, T2 relaxometry had a sensitivity of 100%, specificity of 94.7%, PPV was 91.66% and NPV was 100% and diagnostic accuracy was 96.66% in evaluation of right hippocampi.

In comparison to conventional analysis, T2 relaxometry had a sensitivity of 88.8%, specificity of 83.3%, PPV was 88.8% and NPV was 83.3% and diagnostic accuracy was 86.6% in evaluation of left hippocampi.

In three cases (one right and two left) with normal MR visual analysis findings and 25 cases with positive MR findings, T2 relaxometry levels were increased. Four patients out of the 25 with positive MR visual analysis findings exhibited just FLAIR hyperintensity without volume loss, showed higher T2 relaxometry values indicating early changes in MTS.

Two cases (on the left and one on the right) with positive MR visual analysis findings had normal T2 relaxometry readings, which might be attributed to technical difficulties.

In our investigation, T2 relaxometry exhibited an overall sensitivity of 90%, specificity of 93.3 percent, positive predictive value (PPV) of 93.1 percent, negative predictive value (NPV) of 90.32 percent, and diagnostic accuracy of 91.6 percent.

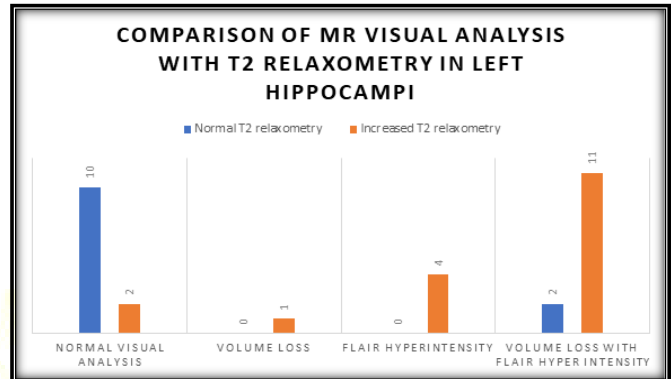
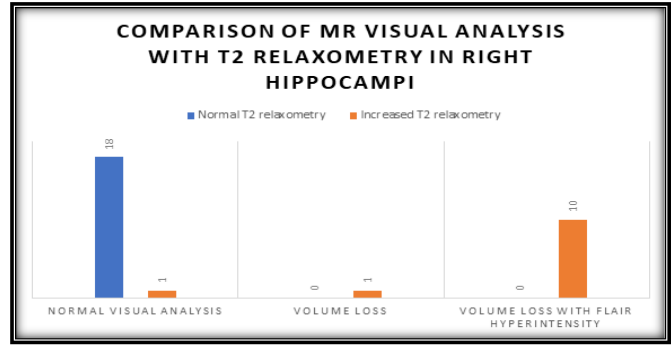
In the study conducted by Chen H et al,^[18] T2 relaxometry had an overall accuracy of 94.1 percent (sensitivity 92.6 percent, specificity 100 percent) in lateralizing the epileptogenic zones. The conclusion reached was consistent with the findings of the current study, which state that T2 relaxometry is feasible in non-invasive lateralization of the epileptogenic focus in detecting MR-negative lesions, allowing for prompt diagnosis and longitudinal disease monitoring.

Coan et al,^[16] compared visual analysis, volumetry, and signal quantification of the hippocampus in 3T MRI to detect hippocampal sclerosis in 2014. According to this study, MRI with expert visual inspection and measurement of hippocampus volume and signal can improve the diagnosis of HS.

In their investigation, Vos SB et al,^[19] discovered that HS patients had extensive volume losses and T2 relaxometry value elevations over length of the afflicted hippocampus and Volumetry and quantitative T2 values in hippocampus region can aid spatially localise hippocampal MRI abnormalities and increase sensitivity of modest localised lesions.

T2 relaxometry was found to be beneficial in detecting the mild type of HS by Sato S et al,^[20] These reactive astrocytes in HS have more cytoplasm and intracellular water, which may help to partially compensate for the volume deficit caused by neuronal cell loss. As a result, minor cell loss may not show up as hippocampal shrinkage, but rather as a T2 signal hyper intense signal caused by the gliosis, which may be identified by T2 relaxometry.

T2-relaxometry was more sensitive than visual analysis of MR images in detecting bilateral hippocampus alterations by Okujava M et al.^[11]



Illustrative cases

**Case 1
Right mesial temporal sclerosis**

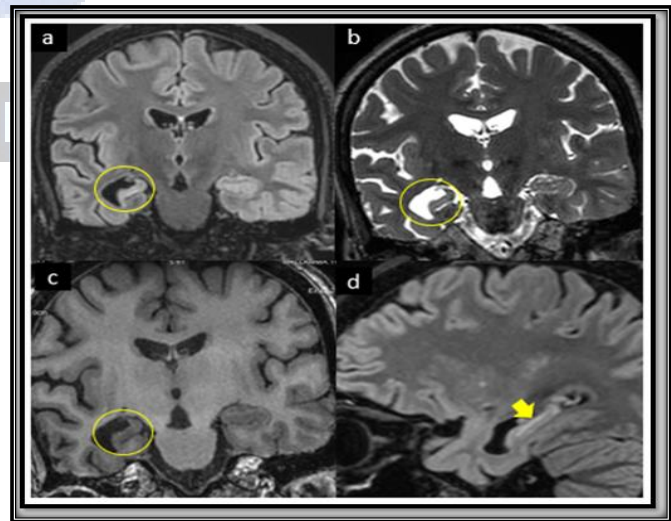


Image 1: a) Coronal FLAIR b) Coronal T2 showing T2/FLAIR hyperintensity with volume loss (yellow circle) of right hippocampus c) coronal FSPGR BRAVO showing volume loss & altered internal architecture with adjacent temporal horn dilatation (yellow circle) of right hippocampus d) Sagittal FLAIR images showing hyperintensity throughout the length of the right hippocampus (yellow arrow).

Management and follow up

In our study, 43.3% of the cases were managed medically, 36.7% of the cases had left ATL+AH, 20% had right ATL+AH.

Out of 17 patients who have undergone surgical resection of

the epileptic focus, 76.4% of the cases were seizure free on anti-epileptic drug (AED) treatment and in 23.5% of the cases there was decreased frequency on AED on one year follow-up.

Case 2

Left Mesial Temporal Sclerosis

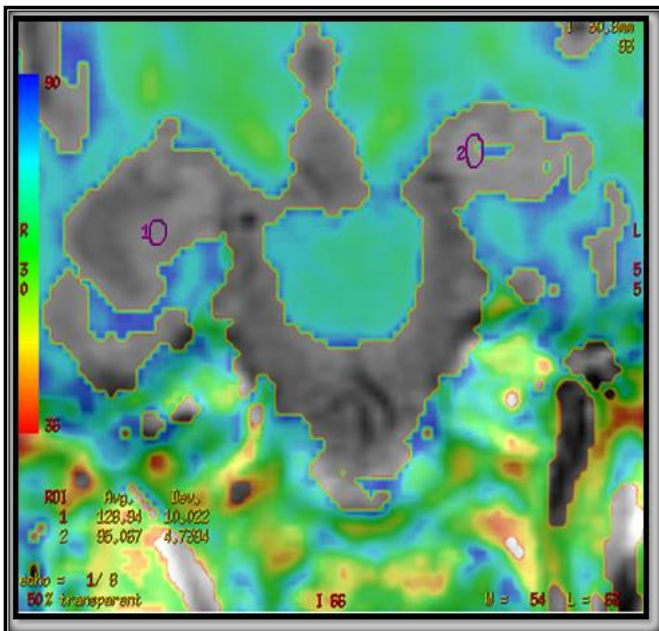


Image 2: T2 relaxometry showing increased values (128.94 ms) in the right hippocampus ROI 1

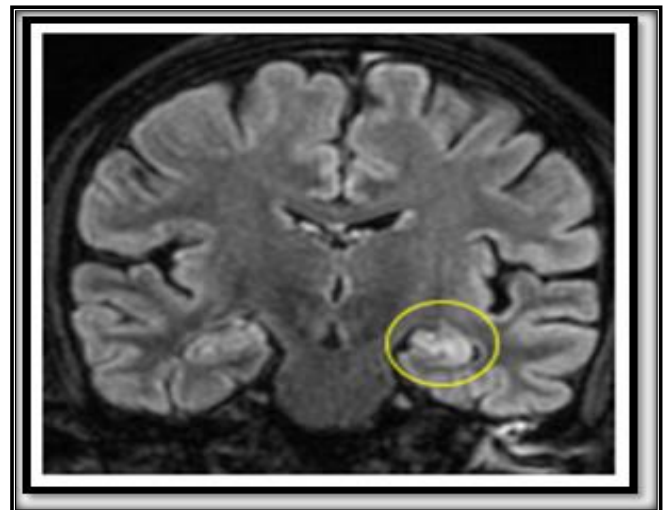


Image 1: Coronal FLAIR image showing FLAIR hyperintensity without volume loss in the left hippocampus (yellow circle)

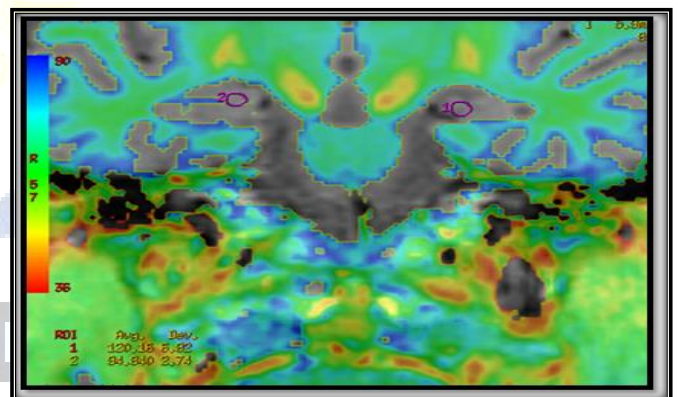


Image 2: T2 relaxometry showing increased values (120.16 ms) in the left hippocampus ROI 1

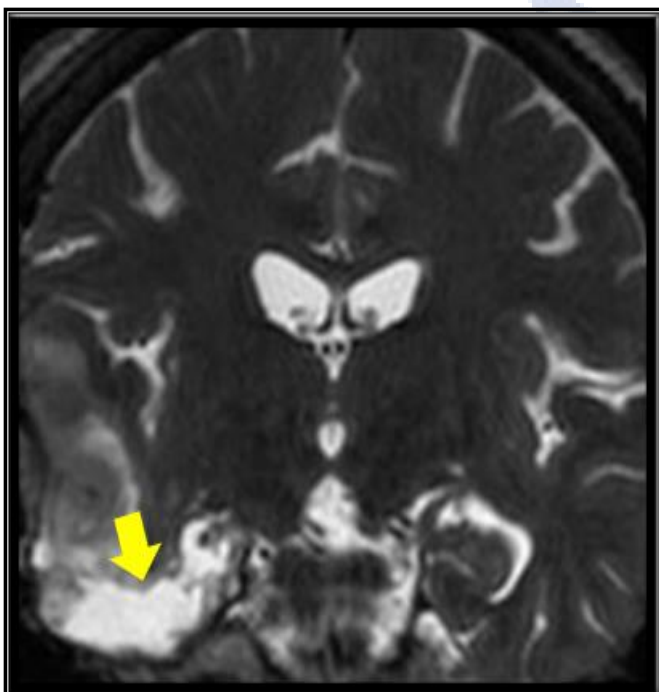


Image 3: Coronal T2 WI after ATL + AH showing postoperative changes (yellow arrow) in the right temporal lobe and hippocampal regions.

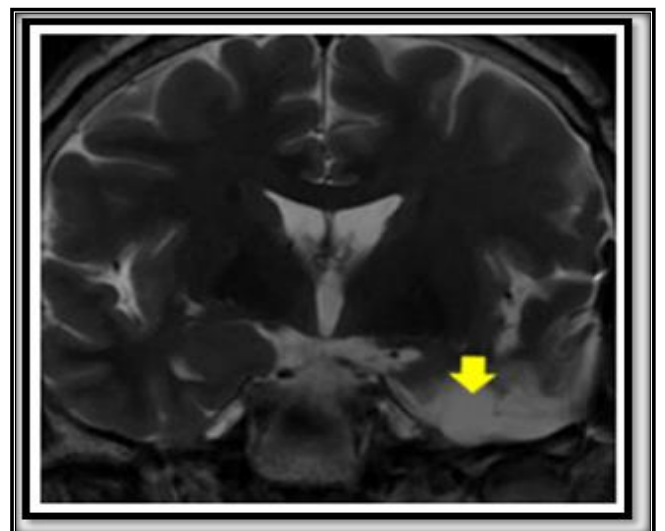
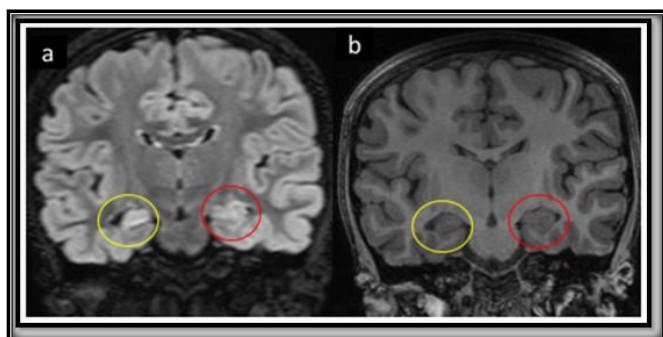


Image 3: Coronal T2 WI showing postoperative changes in the left temporal lobe and hippocampal regions (yellow arrow).

Case 3

Bilateral mesial temporal sclerosis



Case 4

Left mesial temporal sclerosis

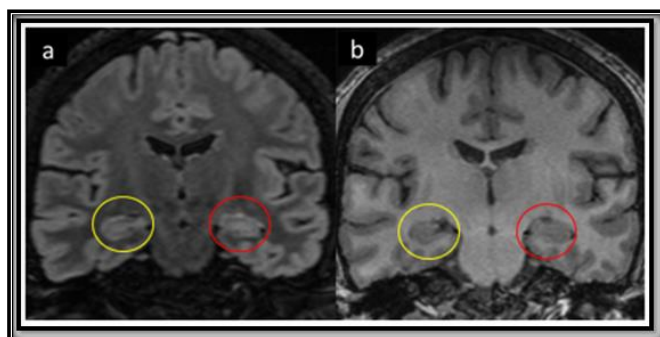


Image 1: a) Coronal FLAIR and b) coronal FSPGR images showing mild volume loss with FLAIR hyperintensity and maintained internal architecture in the right hippocampus (yellow circle) and subtle FLAIR hyperintensity without volume loss in the left hippocampus (red circle).

Image 1: a) Coronal FLAIR and b) Coronal FSPGR images showing bilateral normal hippocampi without any FLAIR hyperintensity or volume loss (right – yellow circle and left – red circle)

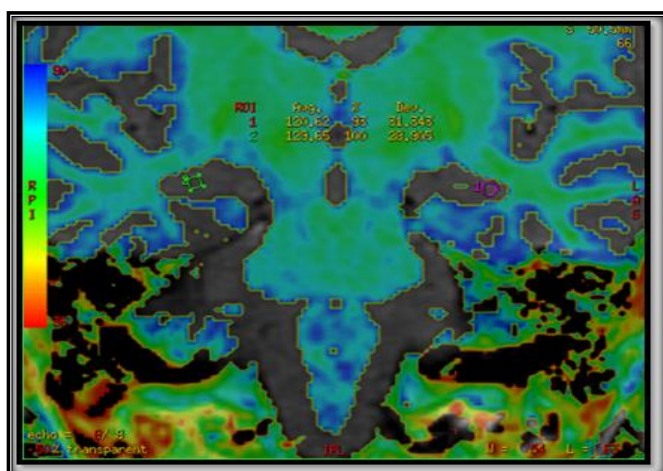


Image 2: T2 relaxometry showing increased values in bilateral hippocampi, ROI 1 – 120.62 ms in the left hippocampus, and ROI 2 – 129.65 ms in the right hippocampus.

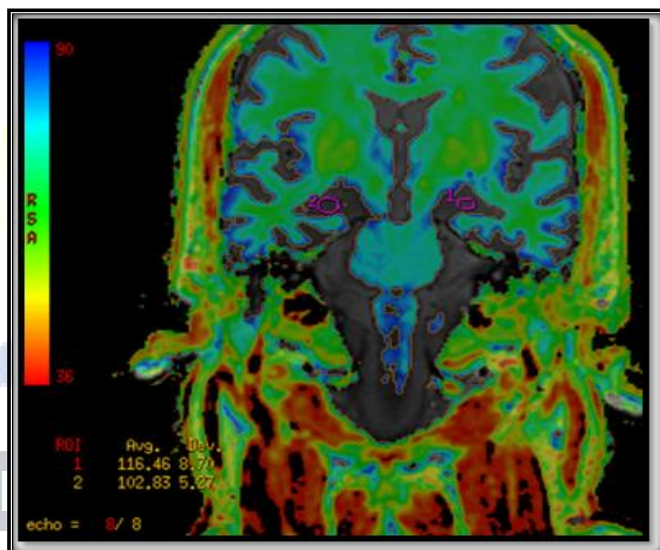


Image 2: T2 relaxometry showing increased values (116.46 ms) in left hippocampus ROI 1

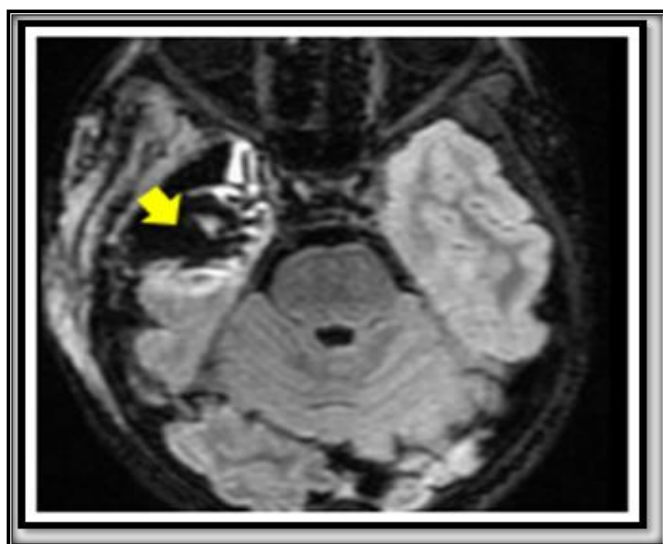


Image 3: Axial FLAIR image showing postoperative changes in the right temporal lobe and hippocampus regions (yellow arrow).

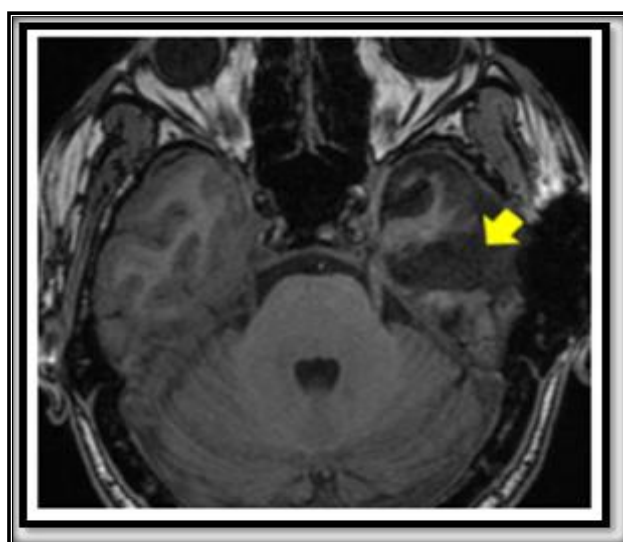


Image 3: Axial FSPGR image showing postoperative changes in the left temporal lobe and hippocampal regions (yellow arrow).

Conclusion

From the observations made in the present study we can conclude that both T2 relaxometry and qualitative MR visual analysis were able to lateralize the epileptogenic zone in patients with MTLE. However, T2 relaxometry demonstrates a superior diagnostic accuracy in detecting HS in three patients with normal visual analysis and four patients showing only FLAIR hyperintensity with no volume loss i.e., T2 relaxometry helped in early detection of seizure focus. It is concluded that quantitative T2 relaxometry has significant role especially in the evaluation of early MTS or cases with no atrophic changes which often escape visual detection.

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