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Hippocampal volumetry and t2 relaxoetry in mesial temporal lobe epilepsy

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Abstract

Introduction: Mesial temporal lobe epilepsy (MTLE) is the most common type of epilepsy in adults. They are generally refractory to medical treatment, so surgery is required usually. Most commonly it is partial type of epilepsy. There are two types of MTLE on the basis of imaging and histopathological findings. The most common pathology of MTLE is hippocampus sclerosis, which can be identified on MRI. Especially sensitivity increases on including quantitative parameters also for hippocampus evaluation.

Aims and Objectives: To evaluate the role of hippocampal volumetry and T2 relaxometry in mesial Temporal lobe epilepsy and correlating these MRI findings with EEG.

Materials and Methods: MRI analysis was done in 40 non-epileptic controls and 40 patients with intractable epilepsy on a 1.5T scanner. On oblique coronal IR/T2W, oblique coronal FLAIR images and16spin-echo pulse sequence; visual assessment, hippocampal volumetry and T2 relaxometry were done, respectively. All cases were correlated with EEG findings for lateralization of the epileptic focus.

Result: Hippocampal volumetry was found to have the highest detection sensitivity (87.5%), followed by T2 relaxometry (77.50%) and visual conventional MRI (67.5%). By combining these modalities, the sensitivity significantly increased to 95%. Two other parameters hippocampal volume ratio (HVR) and hippocampal volume difference (HVD) were included in our study to detect unilateral cases of mesial temporal lobe sclerosis.

Conclusion: Inclusion of T2 relaxometry and hippocampal volumetry increased the sensitivity of the detection of mesial temporal lobe sclerosis.

Keywords: hippocampal volumetry, T2 relaxometry.

Introduction

Epilepsy is a familiar neurological disease. Antiepileptic drugs generally manage most of the epilepsy although in 30% of cases they are not of benefit(1).Epilepsy word was derived from the word Epilepsia which means "to take hold of or to seize" in Greek literature. In ancient cultures of China, Egypt, and India, epileptic seizures were mentioned before. The first book on epilepsy was written almost 2500 years ago by Hippocrates. In that book, the previous

ideas regarding epilepsy aetiology were changed and mentioned excessive phlegm that caused abnormal brain consistency as the cause of epilepsy. Epilepsy is a group of syndromes with different clinical features, not a single disease that was considered before. But in all cases associated with abnormal electrical findings in the brain.[2]. There is pathological electrical activity in neurons of the brain which gives rise to seizure. The main pathophysiology of seizure is relative state of hyper-excitability due to loss of normal regulation of neuronal excitation and inhibition.

Multiple episodes of seizures which are not increased by an acute systemic or neurologic insult for chronic period is considered as epilepsy, however it does not have any specific pathology on its own.[3]

In the adult population, Mesial temporal lobe epilepsy (MTLE) is the most common type of epilepsy[4].Surgery is usually very effective in cases of MTLE, as they are generally refractory to medical treatment [5].However, no sufficient data are known for failure. [6].

In the causes of partial epilepsy, TLE is the most common. On the basis of imaging and histopathological findings there are two types of MTLE[2]: First is TLE with mesial temporal lobe sclerosis (TLE–MTS, about 60–70%), where atrophy and altered MR signals can be seen on imaging and severe neuronal loss in the histological examination, and[7] second is TLE with normal-appearing hippocampus on the MRI (TLE-no, about 30–40%) and on histological examination characterized by no or minimal neuronal loss [7].

The most common pathology of MTLE that is hippocampus sclerosis can be identified on MRI, especially sensitivity increases on including quantitative parameters also for hippocampus evaluation [4].

Bilateral hippocampal sclerosis and mild hippocampal sclerosis which are not detected on visual conventional MRI can be detected using quantitative methods of hippocampus volumetry [4]. Similarly, T2 relaxometry can also increase detection rate of HS on MRI. Histopathological findings of HS have good correlation with quantitative methods like hippocampal volumetry and T2 Relaxometry.

Newer techniques nowadays included in epilepsy protocols like MRI diffusion and MRI perfusions. Another technique like Functional MRI has also included for eloquent cortex mapping and language lateralization in presurgical investigation. Surgery is becoming treatment modality throughout the world for MTLE cases which are refractory to anti-epileptics.[8] Focal and refractory epilepsy is most commonly caused by MTLE. Among these patients 60% have chance of been seizure-free after surgery, therefore identification of the cause on MRI is necessary. Precise localization of seizure focus is critical because of the advent of viable surgical approaches to the management of epilepsy and potential for future less invasive treatment modalities such as gamma knife radiosurgery.

In most of the studies on 1.5 T, MR has shown higher sensitivities of quantitative methods like hippocampal volumetry and T2 Relaxometry in comparison to qualitative methods. Due to new advancements in MRI these days 3T MR is used in many epilepsy higher centers increasing the sensitivity for detection of HS. However there is no significant difference in the hippocampal volume measures of 1.5 and 3T but the quantitative measures in 3T MRI are able to detect

ultra-structural details of HS pathology which are not detected on 1.5 T increasing its sensitivity[4].

Its early diagnosis by using quantitative and qualitative methods of MRI helps in its early treatment. The present study aimed to evaluate the role of hippocampal volumetry and T2 relaxometry in mesial temporal lobe epilepsy, along with correlating these MRI findings with EEG in our set up. On the other hand, we also aim to provide normative MR hippocampal volumetric data for the northeast Indian population.

Aims And Objectives

1. To evaluate the role of hippocampal volumetry in mesial temporal lobe epilepsy.
2. To evaluate the role of T2 relaxometry in mesial temporal lobe epilepsy.
3. Correlating these MRI findings with EEG.

Materials And Methods

It was one-year tertiary care teaching hospital-based case-control study.MRI analysis was done in 40 non-epileptic controls and 40 patients with intractable epilepsy on a 1.5T scanner.

Cases: include MTLE patients presented with a history of seizure and positive EEG Findings.

Controls: include patients with normal EEG and MRI brain. All cases were correlated with EEG findings for lateralization of the epileptic focus.

Inclusion criteria for cases

- Patients of all age groups with a clinical suspicion of mesial temporal lobe epilepsy.

Exclusion criteria for cases

- Infants.
- Patients who did not give consent and were uncooperative.
- Epilepsy due to other causes like intracranial space-occupying lesions (SOLs), meningoencephalitis, granulomatous and demyelinating diseases.

Inclusion criteria for controls:

- Patients of all age groups with normal EEG and MRI brain.

Exclusion criteria for controls

- Infants.
- Patients who did not give consent and were uncooperative.
- Patients with any neurological symptoms.

Approval from the Institutional Ethics Committee (H) was obtained before conducting the study.

Study Protocol

The scheme was started with the patient's serial number, name, age, address, hospital/ MRD number, date of admission and examination. A thorough case history including the clinical examination with symptoms, duration of symptoms, etc. Then these patients were subjected to MRI (SIEMENS MAGNETOM AVANTO 1.5 TESLA whole-body MRI SYSTEM)

Volumetric Analysis: An oblique coronal FLAIR sequence (TR: 9020, TE: 87, slice thickness: 3 mm, interslice gap: 0.3 mm) was obtained perpendicular to the long axis of the hippocampus. Cross-sectional areas of both the hippocampi were measured in these oblique coronal sections by tracing hippocampal boundary manually from hippocampal head to tail. The volumes of both hippocampi were calculated by summing each of the cross-sectional volumes {cross sectional area × (section thickness + interslice gap)}. Normal control values for hippocampal volumes were acquired from control subjects using an identical protocol. Abnormal

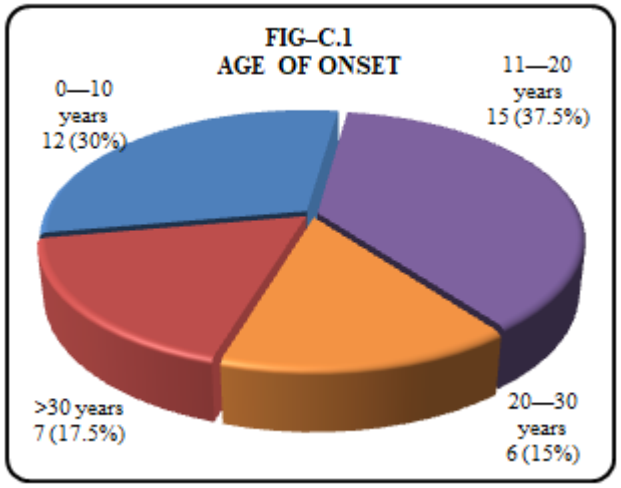
hippocampal volume values were considered when these were both outside the range of all normal control values and more than two standard deviations outside the mean value of control hippocampal volumes.

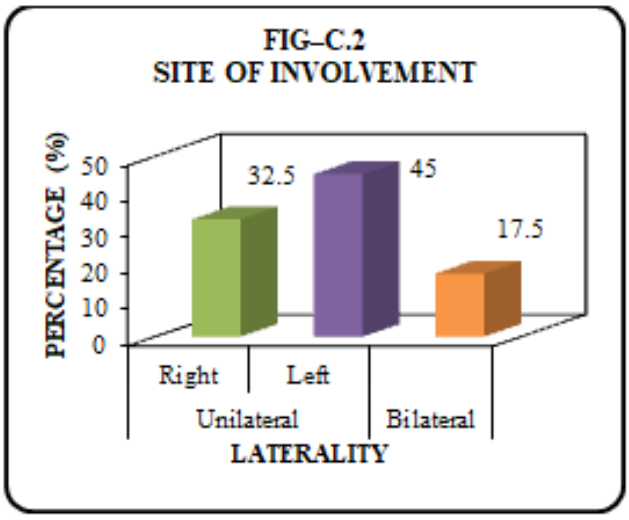
T2 Relaxation Time Measurement: For the computation of T2 values, images were acquired in the coronal plane, ranging from the frontal lobe anteriorly to the fornix posteriorly, using a 16-spin-echo pulse sequence (TE 352 ms; TR 2890 ms, slice thickness 5 mm with 0.5 mm interslice gap). Flow-compensated gradients were used in all three directions. Slices were oriented orthogonal to the hippocampal body. For each individual, averages of 8 slices containing the head, body, and tails of the hippocampus were used to calculate the left and right hippocampal T2 relaxation times (HT2). The values obtained from the control population were used to standardize the normal range for our machine.

Results

In our study, we found no gender difference and MTLE was more prevalent in the adult age group.

Age of onset: Fig–C.1 showed that most of the patients had seizure onset in the second decade of life with a mean age of seizure onset being 17.48 ± 11.31 years. 30% had seizure onset below 10 years, 17.5 % in more than 30 years and 15 % in 20-30 years of age group.

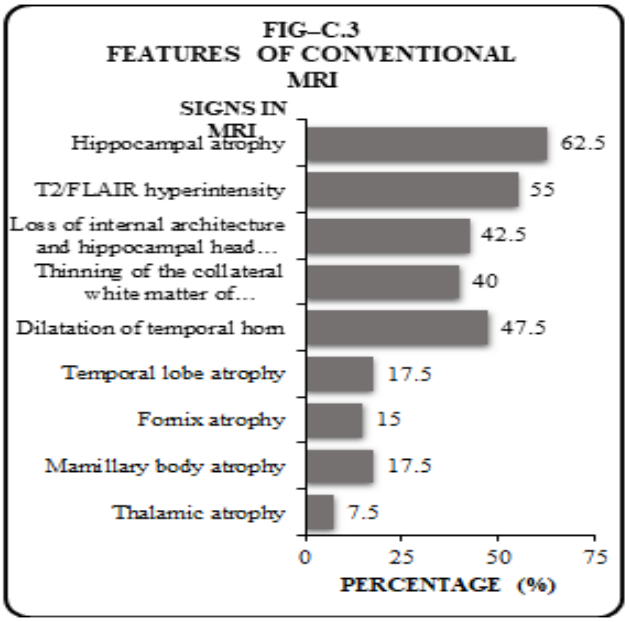




Site of involvement: Fig–C.2 showed that 13 out of 40 cases involved the right hippocampus, 18 out of 40 cases involved left hippocampus and 7 cases had asymmetrical bilateral hippocampi involvement.

Features of conventional MRI: Fig–C.3 showed that hippocampal atrophy (25 out of 40 cases) and T2/FLAIR hyperintensity (22 out of 40) were most commonly identified features in mesial temporal sclerosis, followed by dilatation of temporal horn, loss of hippocampal internal architecture & head digitations and thinning of collateral white matter in parahippocampal white matter. Of the extra temporal changes, Mammillary body atrophy was most

commonly seen in 7 patients followed by fornix atrophy and 3 cases of thalamic atrophy.



T2 relaxation time: In the control group mean T2 relaxation value was 103.33 ms for the right hippocampus and 104.35msfor the left hippocampus. A value 2 SD above the mean (116.5 and 117.07 ms for right and left respectively) was taken as cut off value for normal T2 relaxation for our machine. In cases, according to table C.1, we found, mean T2 relaxation value in the right and left abnormal hippocampi was 130.1ms and 128.17ms respectively. As P values were less than 0.0001, so the values were statistically highly significant.

Table: C.1 (T2 Relaxation Time)

T2 Relaxation Time	Case			Control		
	Number (n)	Mean	± S.D.	Number (n)	Mean	± S.D.
Right Hippocampus	16	130.1*	7.69	40	103.33	6.6
Left Hippocampus	21	128.17*	5.83	40	104.35	6.36

*Mean values of all the abnormal T2 Relaxation Time

Hippocampal volume: Similar to T2 relaxometry the average hippocampal volume was 3.08 cc for the right hippocampus and 3.05 for the left hippocampus in control patients. A value 2 SD below the mean (2.78 cc and 2.72 cc for right and left respectively)was taken as cut off value for normal hippocampal volume for our study. In cases according to table C.2, we found, mean hippocampal volume in the right 24 and left 29 abnormal hippocampi were 2.19 ± 0.14 cc and 2.10 ± 0.10 cc respectively. As P values were less than 0.0001, so the values were statistically highly significant.

Table C.2 (Hippocampal Volume)

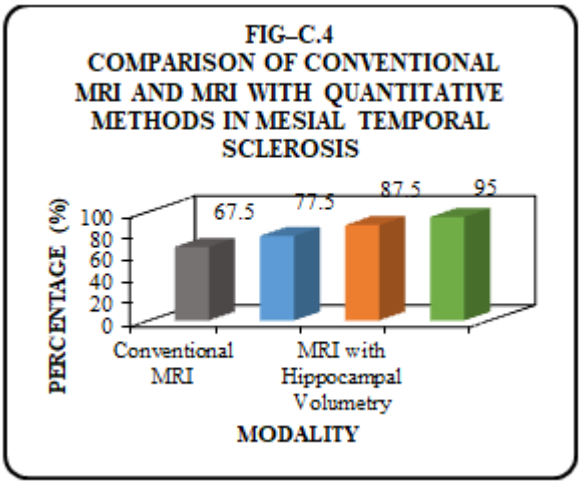
Hippocampal Volume	Case			Control			p value
	Number (n)	Mean	± S.D.	Number (n)	Mean	± S.D.	
Right Hippocampus	24	2.19*	0.14	40	3.08	0.15	<0.001
Left Hippocampus	29	2.10*	0.10	40	3.05	0.16	<0.001

**Mean values of all abnormal hippocampal volume of the affected side*

Hippocampal volume difference and ratio: We also calculated hippocampal volume difference and hippocampal volume ratio found as 0.15 cc and 0.95 respectively in the control group. A value 2 SD above the mean of HVD (0.3 cc) and 2SD below the mean of HVR (0.91) was taken as a cut-off to diagnose all the unilateral cases of MTLE. By this, we were able to detect 29 unilateral cases of MTLE.

Table: C.3 (Hippocampal volume difference and ratio)

Hippocampal Volume	Case			Control			p value
	Number (n)	Mean	± S.D.	Number (n)	Mean	± S.D.	
Hippocampal Volume Difference	29	0.98	0.20	40	0.15	0.08	<0.001
Hippocampal Volume Ratio	29	0.69	0.05	40	0.95	0.02	<0.001



Comparison of conventional MRI, MRI with T2 relaxometry, hippocampal volumetry and combined modality in mesial temporal sclerosis detection: Table-C.4 showed a relaxometry, hippocampal volumetry and combined modality of all three approaches concerning interictal scalp EEG which was the gold standard in our study for detection of mesial temporal lobe sclerosis. Conventional MRI was able to detect only 27 cases of MTLE. MRI combined with T2 relaxometry was able to detect 31 cases of suspected

mesial temporal sclerosis. MRI combined with hippocampal volumetry detected 35 cases. However, MRI combined with both T2 relaxometry and hippocampal volumetry was able to detect the highest number of MTLE cases, 38. Therefore, the total sensitivity of MRI combined with both T2 relaxometry and hippocampal volumetry was 95% for the detection of MTLE.

Discussion

15 cases (37.5%) showed seizure onset in the age group range of 11-20 years, followed by 12 cases (30%) in the age group of 0-10 years, 7 (17.50%) in the age group of >30 years and least 6 cases (15%) in age group range of 20-30 years.

Therefore, we got our mean age of seizure onset of 17.48 ± 11.31 years. A.C. Coan *et al* (2009)[9]in their study of 33 patients found the median age of onset of 12.3 years, which was in concordance with our study median age of seizure onset, 16.5 years.

We found 13 cases (32.50%) of the right side MTLE and 18 cases (45.0%) of the left side MTLE. Rest 9 cases out of 40 cases, 7 showed bilateral involvement of hippocampus and the remaining 2 did not show involvement of the hippocampus on MRI evaluation. Thus, left-sided MTLE was found to be more common than right-sided MTLE in our study. B. Kubota *et al* (2014)[4] and A.C. Coan (2009)[9] in their related study-also found left-sided MTLE more common than the right-sided MTLE.

Conventional MRI findings that were found in MTLE cases were broadly divided into two type's primary and secondary findings as described in the text. The primary findings which include hippocampal atrophy and T2/FLAIR hippocampal hyperintensity were found in 62.50 % (25 cases) and 55 % (22 cases) of patients respectively. These findings resembled with the study of E. Kobayashi *et al* (2004) where T2 hippocampal signal abnormalities were found in 79 (52%) subjects and Hippocampal atrophy was found in 90 (59%) individuals[10] and another study of Paramdeep Singh *et al* (2013) where they found an increased signal on T2w in 50% cases and hippocampal atrophy in 56.7% cases. [11]

In our study in a group of secondary findings, the most common finding we found was the Dilatation of temporal horn (47.50%) in 19 cases. 2nd most common secondary finding we found was Loss of internal architecture and hippocampal head digitations (42.50%) in 17 cases, followed by the Thinning of the collateral white matter of Parahippocampal gyrus in 16 cases (40 %).

In extra-temporal findings, mamillary body and temporal lobe atrophy were found in the same number of cases, 7 out of 40 cases, constituting 17.50%. Other findings like fornix atrophy and thalamic atrophy were found in 6 (25%) and 3 (7.50%) cases respectively out of a total of 40 MTLE cases.

T2 relaxation time in normal patients

It was a quantitative variable taken in our study which was measured in both rights and left hippocampus in normal patients and MTLE cases. We found mean T2 relaxation time of right and left hippocampus in normal patients as 103.33± 6.6ms and 104.35± 6.36ms respectively. We had taken mean + 2SD of these values as cut off for our cases, to call them abnormal. Therefore, for right and left hippocampus 116.5ms and 117.07 ms were taken as cut-off respectively.

T2 relaxation time in MTLE patients

On considering the above-mentioned parameters we found 16 cases which showed an increase in T2

relaxation time in right hippocampus ranging from 121 to 144.9ms and the calculated mean was 130.10± 7.69ms for the right hippocampus.

Similarly, for the left hippocampus, we found an increase in T2 relaxation time in 21 cases with T2 relaxation time ranging from 119 to 142 ms and a mean of 128.17± 5.83ms.

Therefore, mean T2 relaxation time was more in the right abnormal hippocampus as compared to the left abnormal hippocampus.

Above mentioned findings of our study were correlated with the study of Gavin Winston *et al* (2017) who found significantly lower mean hippocampal T2 values on the left than the right, with both automated and manual methods.

Their hippocampal T2 mean value was indistinguishable between the left (127.7 msec) and right (128.1 msec) hippocampi individually.[12]

Hippocampal volume in normal patients

By calculating the normal hippocampal volume in the normal control group we were able to give normative data for hippocampal volume for normal eastern India population that can be used in the management of patients with medically refractory epilepsy. Here, in our study, we found normal mean hippocampal volumes of both right and left hippocampus were 3.08± 0.15 cc and 3.05± 0.16 cc respectively.

Hippocampal volume value ≤2 SD below these mean control hippocampal volumes of 2.78 cc and 2.72 cc for right and left respectively were considered abnormal. No difference was found between men and women, and no correlation was found with the age of control volunteers, the same as that of T2 relaxometry.

Hippocampal volume in MTLE patients

Concerning the control group cut-off, we detected hippocampal volumes were lower in 24 cases on the right side and 29 cases on the left side.

We had included all the bilateral cases with decreased hippocampal volume also and calculated the mean for each side. The mean hippocampal volume for right-sided MTLE was 2.19±0.14 cc and for left-sided MTLE was 2.10±0.10 cc.

Our findings were in resemblance with the study done by Gavin P. Winston *et al* (2017) on 50 cases of MTLE and 50 controls[12]

Another study of L Bonilha*et al* (2003)[13] on 25 patients with drug-refractory MTLE found near about similar hippocampal Volume.

Hippocampal volume ratio and hippocampal difference

Two new parameters were included in our study in which one was hippocampal volume ratio which was calculated by division of smaller to larger hippocampal volumes. In the control group, the value of HVR ranged from 0.92 to 0.99, and from these mean was calculated and value <2SD of mean was taken as cut-off (<0.91) for diagnosis of unilateral hippocampal atrophy. Another parameter was HVD which was calculated by subtracting right-left hippocampal volume and the mean of HVD in controls was found to be 0.15 ± 0.08 cm3 (0.03–0.26 cc). All the values which fall outside the >2SD upper limit of the range (0.3 cc) were considered abnormal.

Using this criterion, we were able to detect 29 out of 35 (82.9%) TLE patients who had HVD of more than 0.3 cc and HVR less than 0.91. The rest of the 6 patients had bitemporal abnormalities which were detected by

EEG and quantitative methods of MRI studied hippocampal volumetry or T2 relaxometry.

These findings were in resemblance to the study of Paramdeep Singh *et al* (2013). [11]

Comparison of qualitative and quantitative assessments

After combing all the primary and secondary findings of conventional MRI we were able to detect a total of 27 cases out of 40 cases. Giving sensitivity of conventional MRI alone of 67.50 %. A familiar study was byAbdel Aziz Kamal Aun*et al* (2015) where they were able to detect 60% cases by conventional MRI. [14]and another study of Paramdeep Singh *et al* (2013) where 65% sensitivity was found in concordance with EEG. [11]

We were able to detect 4 more cases of MTLE by using T2 relaxometry. In all we were able to detect 31 cases out of a total of 40 cases of MTLE, giving the sensitivity of T2 relaxometry in concordance with EEG as 77.50%. This was relatable with Paramdeep Singh *et al* (2013)[11] study whereby T2 relaxometry 14 cases were detected out of 20 cases of MTLE, giving the sensitivity of T2 relaxometry 70% in concordance to EEG.

Then the last parameter we had used was hippocampal volumetry by which 8 more cases were detected which did not show any findings on conventional MRI and 7 more cases which were negative on T2 relaxometry out of which most of them were bilaterally affected MTLE. However, 3 cases detected by T2 relaxometry were negative on hippocampal volumetry.

Hippocampal volumetry in all was able to detect 35 cases of MTLE, giving its sensitivity of 87.50%. Similar results were found in Paramdeep Singh *et al* (2013)where they found the sensitivity of hippocampal volumetry alone was 75%.[11]

In all on combining all MRI quantitative and qualitative parameters, we were able to detect 38 cases out of 40 cases and 2 cases were MRI negative. So, combining sensitivity becomes 95 %.

A study of NikdokhtFarid*et al* (2012)[15] revealed that quantitative MR imaging depicted HA in patients at rates that may exceed those based on visual inspection of the clinical MR imaging study (88% vs 76%).

Conclusion

In our study, we found no gender difference and MTLE was more prevalent in the adult age group. Lesions were more widespread in the left hemisphere. In conventional MRI primary and secondary features can be seen to detect MTS. Hippocampal atrophy was the most common and T2/FLAIR hyperintensity was the second most common primary sign of MTS in our study. Secondary MR Findings seen in mesial temporal sclerosis gave suspicion in mild cases and bilateral cases, increasing the sensitivity; however, they were not sensitive predictors of this entity by themselves.

Hippocampal volume measured in the control group can be used as normative data that would apply to the management of Indian patients with medically refractory epilepsy. Right and left hippocampal volumes were positively correlated, and the right hippocampal volume was larger than left by a statistically insignificant amount. No significant correlation of hippocampal volumes and T2 relaxation times existed with gender or age. Patients with intractable temporal lobe epilepsy had smaller mean hippocampal volume and longer T2 relaxation time ipsilateral to the seizure focus. Hippocampal volumes

and T2 values correlated inversely with each other in TLE cases.

HVR and HVD were the new two parameters that were diagnostic of unilateral MTS. There was an increase in the sensitivity of detection of MTS in epilepsy patients on including Quantitative methods like T2 relaxometry and Hippocampal volumetry with conventional MRI. Especially these were more sensitive in diagnosing bilateral pathologies and mild unilateral pathology. Among all modalities tested in our study, hippocampal volumetry proved to be the most sensitive giving87.5% lateralization.

Hippocampal volumetry and T2 Relaxometry are the quantification methods that are easily available nowadays. Therefore can be used routinely for the detection of MTLE cases. Other new modalities are in research for the detection of MTS not used commonly like MRS, Diffusion MR, Perfusion MRI, Functional MRI, etc. However, confirmative or specific diagnostic modality is always pathological diagnosis by HPE after surgery of the patient.

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