

Original Research Article

Role of hippocampal volumetry in drug resistant epilepsy

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Received: 04 July 2019

Accepted: 17 July 2019

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ABSTRACT

Background: Hippocampus is a brain structure located deep in the temporal lobe. The structure is crucial for learning and memory and is a natural inhibitor of seizure activity in brain. In drug resistant epilepsy (DRE), there is shrinkage of the hippocampus leading to poor seizure control.

Methods: Patients meeting the diagnostic criteria for drug resistant epilepsy between the age group of 10-60 years were enrolled in the study. Epileptic non drug resistant controls and normal healthy individuals were taken from same cohort. Selected patients underwent MRI Brain and their hippocampal volumes were estimated manually. Coronal oblique sections, perpendicular to the long axis of hippocampus were taken and hippocampal volume (HV) were calculated using region of interest approach with manual delineation .

Results: There was increment in detecting hippocampal atrophy from 30% to 46.6% in DRE patients when manual hippocampal atrophy was used in addition to visual assessment. The mean right and left hippocampal volumes in drug resistant epilepsy cases were found to be 2.17+0.57 cc and 1.52+0.54 cc respectively. Left HV was found to be statistically significantly smaller than right side (p value < 0.05). DRE patients had smaller mean bilateral HV than healthy controls, the difference being 33%. The left HV loss was almost double the right HV loss among DRE cases. The hippocampal volumes were reduced in DRE patients compared to epileptic non-resistant patients; however the difference was found to be less than that of normal healthy controls.

Conclusion: Manual hippocampal volumetry detected more patients with hippocampal atrophy in our study compared to visual assessment. Manual hippocampal volumetry should be routinely done in patients with Drug resistant epilepsy.

Keywords: Drug resistant epilepsy, Epilepsy, hippocampal volume, Manual hippocampal volumetry

INTRODUCTION

Hippocampus is a brain structure located deep in the temporal lobe which is crucial for learning and memory.¹⁻² Hippocampal anatomy has been meticulously studied in the past and the relevance lies in the clinical consequences of hippocampal atrophy.¹ Epilepsies present a broad group of disorders where the usefulness of hippocampal volume measurement is being intensively studied. Hippocampus has been considered the primary

seizure generator in temporal lobe epilepsy.³ Hippocampus has an inhibitory effect on seizures and as it gets damaged, seizures become more intractable.¹ Up to 50% to 75% of patients with epilepsy may have hippocampal sclerosis.¹ In drug resistant epilepsy, there is shrinkage of the hippocampus leading to poor seizure control. It has been described as the earliest and most severely affected structure in epilepsy.¹ Subtle hippocampal atrophy can characterize early disease, which is often missed during routine visual inspection. Quantitative measurements of hippocampal volume can

improve sensitivity by detecting subtle and bilateral abnormalities.

Surgical resection of the hippocampus is the most successful treatment for medication-refractory medial temporal lobe epilepsy due to hippocampal sclerosis.¹ Quantitative assessment of hippocampus has potential to become prognostic marker of surgical management. Using a classification based on presence or absence of HA based on volumetry, patients achieving an excellent postoperative seizure outcome were significantly more likely to have HA.⁴ Patients with bilateral or no HA based on volumetry are significantly less likely to attain seizure freedom after surgery relative to patients with clear unilateral HA, although satisfactory postoperative outcomes in patients with bilaterally symmetric hippocampal volumes are achievable.⁴

Quantitative assessment of hippocampus can detect the presence and lateralise HA in TLE and may enhance standard visual analysis, providing a means for translating volumetric analysis into clinical practice.⁵ Visual rating is semi quantitative, and practical but a crude method of rating atrophy. Measurement of hippocampal volume can be done using automated software or by manually outlining hippocampal volumes.

Hippocampal volume loss is a sensitive and specific pointer of hippocampal sclerosis in the clinical setting of epilepsy, and hippocampal volumetric study can quantify atrophy in TLE patients.⁶ Additionally, the drug resistant epilepsy patients is a special subset that needs special care while interpreting hippocampal volume data as the effects of seizures on hippocampus are perhaps a function of several parameters or predictors.⁷ In clinical practice, there is a common dilemma regarding lateralization of epilepsy on MRI, in cases of bilateral sclerosis and MR normal MTS. A size difference in relation to the apparently normal hippocampus, fails in these situations, thus comparison with a normative data becomes essential.⁸ However, the quantitative measurement data from Indian subcontinent is sparse.

The present study was done to know hippocampal volumes in patients with drug resistant epilepsy and compare the same with epileptics on regular medications. Normal healthy controls were also taken for comparison.

METHODS

Subjects

The study was conducted in the Department of Radiodiagnosis at Postgraduate Institute of Medical Education and Research and Dr. Ram Manohar Lohia Hospital.

Patients meeting the diagnostic criteria for drug resistant epilepsy as per ILAE between the age group of 10-60 years were enrolled in the study.⁹ Study participants

included a total of 30 cases of drug resistant epilepsy patients and 8 cases of epileptic patients controlled on regular medications. 30 normal healthy controls were included to obtain the comparative data. Written informed consent was taken from the patients or their legal guardian for inclusion in the study. The study was approved by institutional ethics committee.

All the patients were screened for inclusion and exclusion criteria and selected patients had their clinical, electroencephalographic and laboratory investigations done. All the recruited patients underwent MRI Brain using a dedicated Epilepsy protocol in Siemens 3.0 Tesla (Magnetom Skyra) MR system using standard head coil. Study design was cross sectional observational study.

Study duration was the study lasted for 2.5 years (November 2015 to March 2017).

Inclusion criteria

Cases

Patients less than 60 yrs of age with drug resistant epilepsy diagnosed as per International League Against Epilepsy (ILAE) criteria⁹. The exclusion criteria are given in Table 1.

Table 1: Exclusion criteria for present study dementia.

Major psychiatric illness
Post traumatic epilepsy
History of alcohol or substance abuse.
History of long term steroid use
Childhood Absence seizures
Patients with general contraindications of MRI
Unwilling to give consent for the study

Controls

Patients presenting in the Radiology department undergoing MRI Brain for other indications were taken as healthy age and sex matched controls. Patients with seizures controlled on anti-epileptic drugs were taken as epileptic controls.

Image acquisition

Magnetic resonance imaging was performed using Siemens 3.0 Tesla (Magnetom Skyra) MR system using standard head coil. The subjects underwent MRI evaluation using the protocol detailed below:

Manual delineation of hippocampus

A 3-dimensional T1W imaging was acquired using Fast Low Angle Shot (FLASH MRI). Images perpendicular to the long axis of the hippocampus, oblique coronal section

(slice thickness 1 mm and interslice gap of 0.5 mm) were taken for measurements by outlining the region of interest (ROI) manually on a magnified image. The white matter structures near hippocampus e.g. alveus and fimbria were excluded. The hippocampus was delineated using anatomical landmarks as described below.⁸

Superiorly

The alveus and the cerebrospinal fluid (CSF) within the lateral ventricle.

Inferiorly

The white matter of the parahippocampal gyrus below the subiculum.

Laterally

The CSF in the lateral ventricle.

Superomedially

CSF in the cisterna ambiens.

Inferomedially

Extend the inferior border of the cornu ammonis medially, with a straight horizontal line and considered all tissue above as hippocampus and below as parahippocampal cortex.

Anteriorly

The alveus, as an internal landmark, in combination with the appearance of CSF of the lateral ventricle, as an external landmark, to delineate the hippocampus from the amygdala.

Posteriorly

The lateral ventricle is used as an external landmark and the posterior end is localized in the slice, where an ovoid grey matter starts to appear inferomedial to the trigone of the lateral ventricle.

The borders of the hippocampi were manually traced sequentially with a mouse-driven cursor on each slice from the posterior to anterior till the entire length of hippocampus.

Hippocampal volume calculations

Hippocampal volume was calculated by summing up the area that had been delineated using the manual cursor. Area thus obtained was multiplied by 0.15 (1mm slice thickness and 0.5 mm inter-slice gap), giving values in cubic centimeters.

RESULTS

A total of 30 drug resistant epilepsy patients with mean age 22.26 ± 12.16 years (M:F=14:16) were recruited.

Out of 30, 14 (46.6%) drug resistant patients had reduced hippocampal volumes on manual hippocampal volumetry (MHV). Reduced volumes were seen on left side in 9 (30%) patients, on right side in 1(3.3%) patient and bilaterally in 4 (13.3%) patients (Table 2).

Table 2: No. of DRE patients with reduced hippocampal volume using manual hippocampal volumetry (MHV) and their distribution according to location (N=30).

HA	No. of cases	Percentage
Present	Right	1 3.3%
	Left	9 30%
	Bilateral	4 13.3%
Absent	16	53.4%
Total	30	100%

Out of 30 DRE patients, 46.6% cases of HA were seen using manual hippocampal volumetry. A total of 30% cases were found to have left HA on manual hippocampal volumetry, out of which 88.9% were also detected by visual assessment and 11.1% additional cases were detected by MHV. Only 3.3% cases were found to have right HA on MHV which were previously diagnosed on visual assessment also. MHV revealed bilateral HA in 13.3% DRE cases which were not seen visually.

The mean right and left HVs in drug resistant epilepsy (DRE) cases were found to be 2.17 ± 0.57 cc and 1.52 ± 0.54 cc respectively. The difference between right and left HV was found to be statistically significant using t-test calculator for two independent means i.e. left HV was found to be statistically significantly smaller than right side with p value=0.000043 (p value <0.05).

Table 3: Mean right HV and left HV (in cc) in healthy controls and DRE cases.

Mean HV	Healthy controls (N=30)	DRE Cases (N=30)	Difference
Right HV (cc)	2.77	2.17	21.6%
Left HV (cc)	2.73	1.52	44.3%

Comparison of HV of healthy controls and DRE patients was done (Figure1 and 2, Table 3). HVs in normal, healthy patients (n=30) was 2.73 ± 0.52 cm³ (L) and 2.77 ± 0.6 cm³ (R) and in those who had DRE (n=30), HV was 1.52 ± 0.5 cm³ (L) and 2.17 ± 0.57 cm³ (R). The Mean bilateral HV was found to be 2.75 ± 0.48 cc in normal healthy controls and 1.84 ± 0.56 cc in DRE cases.

There was a difference of 33% between control and DRE group. The right HV was found to be 2.77+0.43 cc in normal, healthy controls and 2.17+0.57cc in DRE cases. There was 21.6% right HV loss in the DRE group.

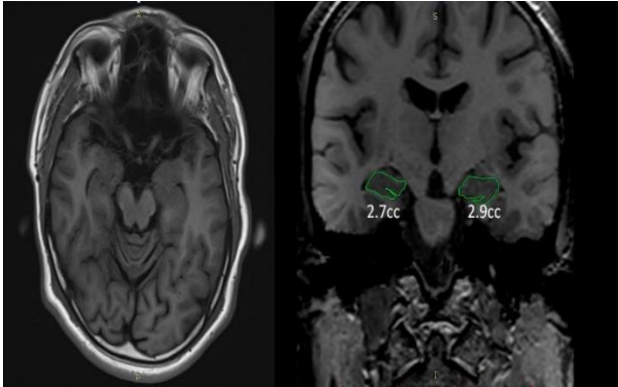


Figure 1: T1W axial and coronal magnified image calculating hippocampal volume in healthy control.

The left HV was found to be 2.73+0.53 cc in controls and 1.52+0.54cc in DRE cases. There was 44.3% left HV loss

in the DRE group. So the left HV loss (44.3%) was almost double the right HV loss (21.6%) among DRE cases (Figure 3). Left side correlation was better compared to right with perhaps due to presence of pathology on left side in most of the cases.

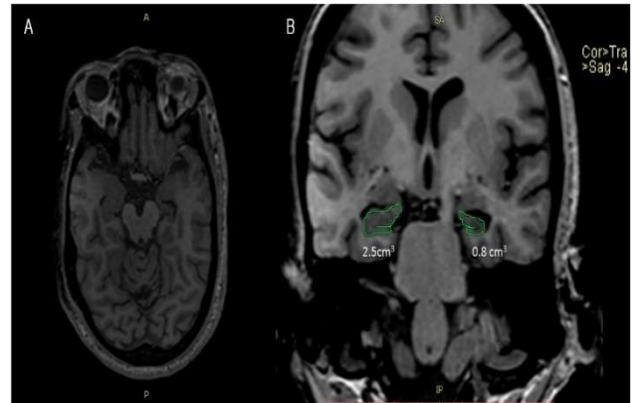


Figure 2: T1W axial and coronal magnified image with reduced left hippocampal volume in a patient of drug resistant epilepsy.

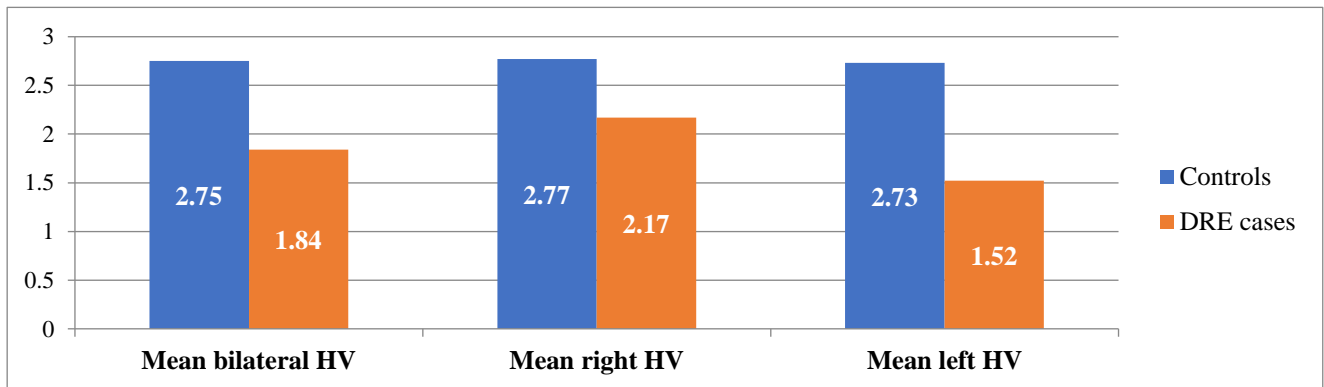


Figure 3: Mean bilateral, mean right HV and mean left HV (in cc) in healthy controls and DRE cases.

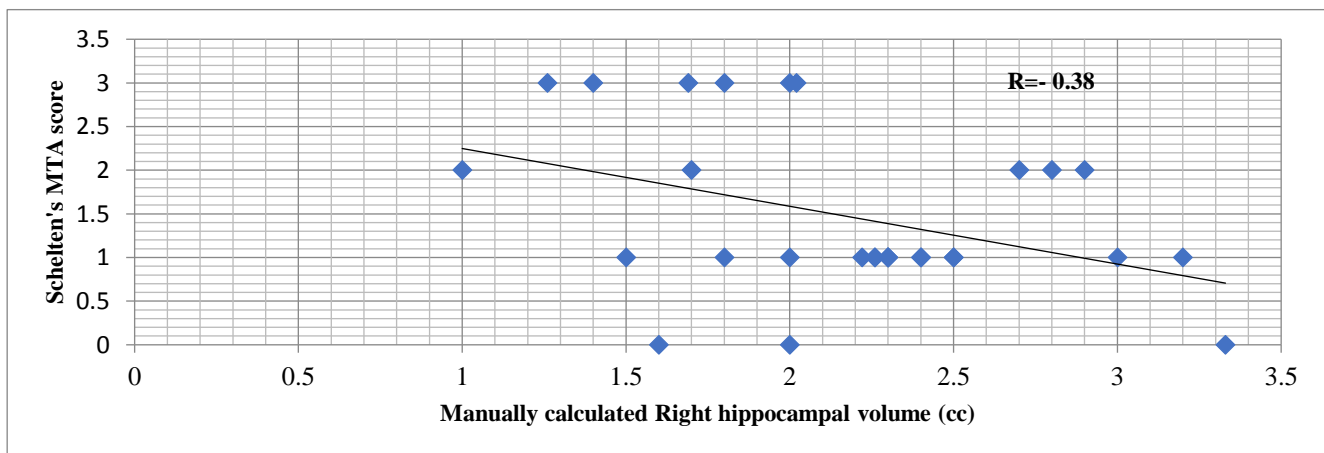


Figure 4: Correlation between MTA score and MHV in DRE cases on right side (N=30).

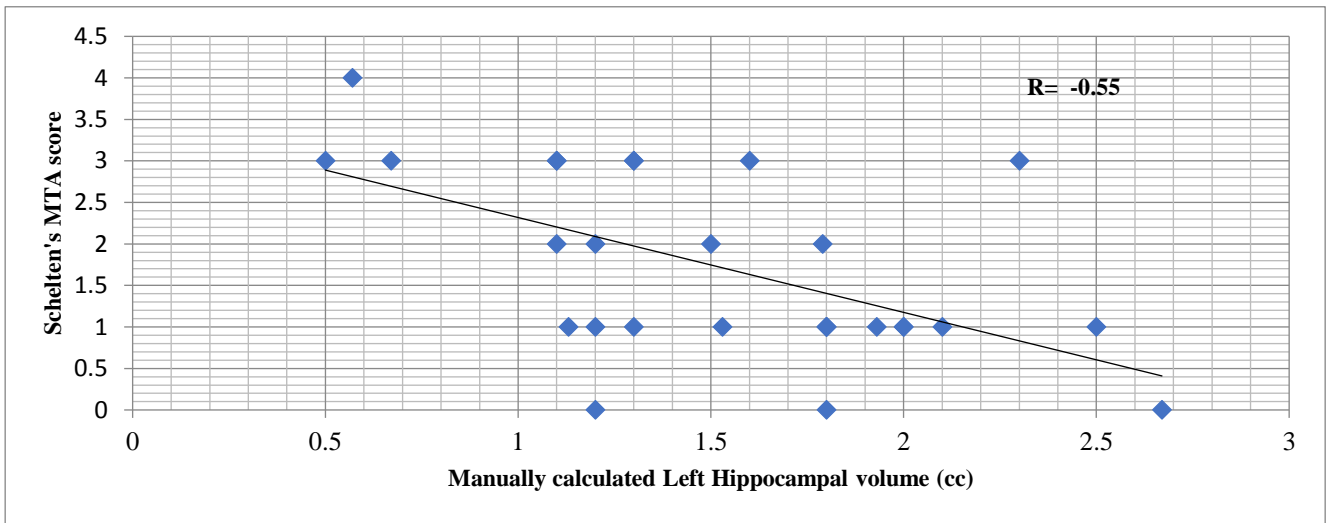


Figure 5: Correlation between MTA score and MHV in DRE cases on Left side (N=30).

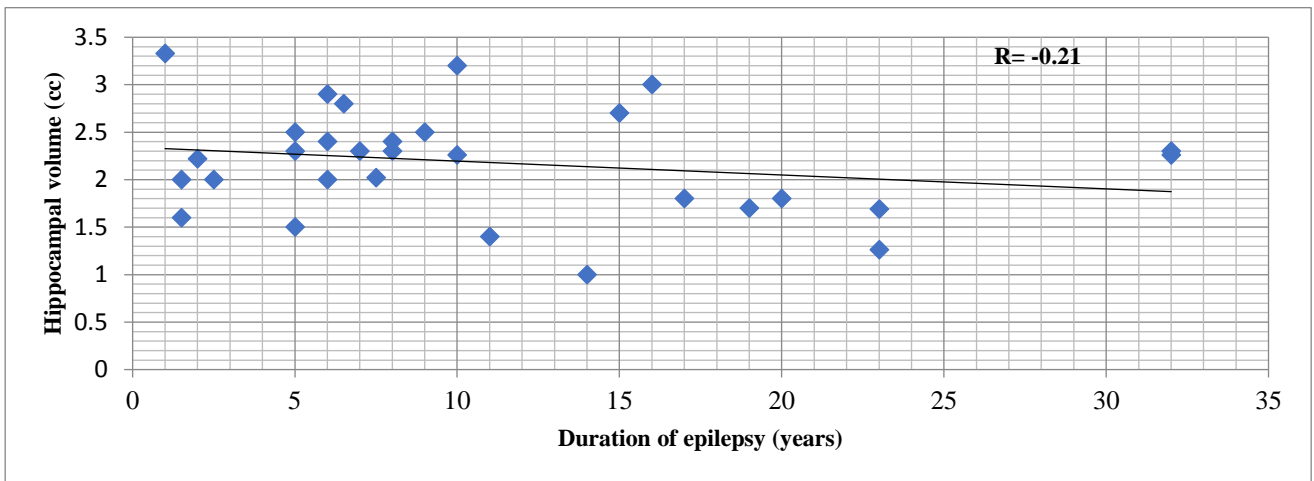


Figure 6: Correlation between duration of epilepsy (in years) and manually calculated HV on right side in DRE cases (N=30).

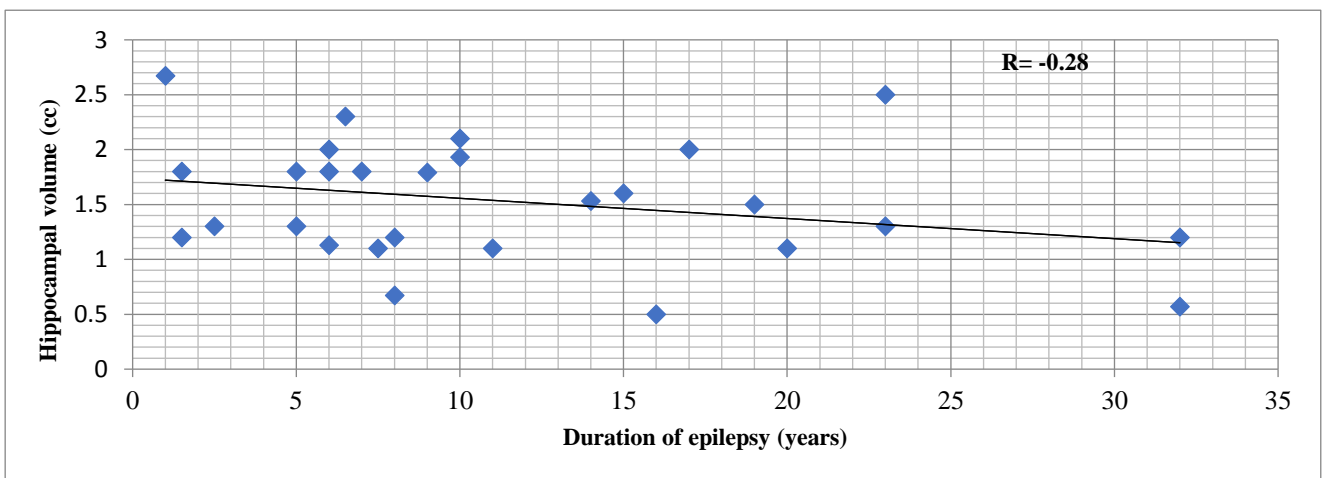


Figure 7: Correlation between duration of epilepsy (in years) and manually calculated HV on left side in DRE cases (N=30).

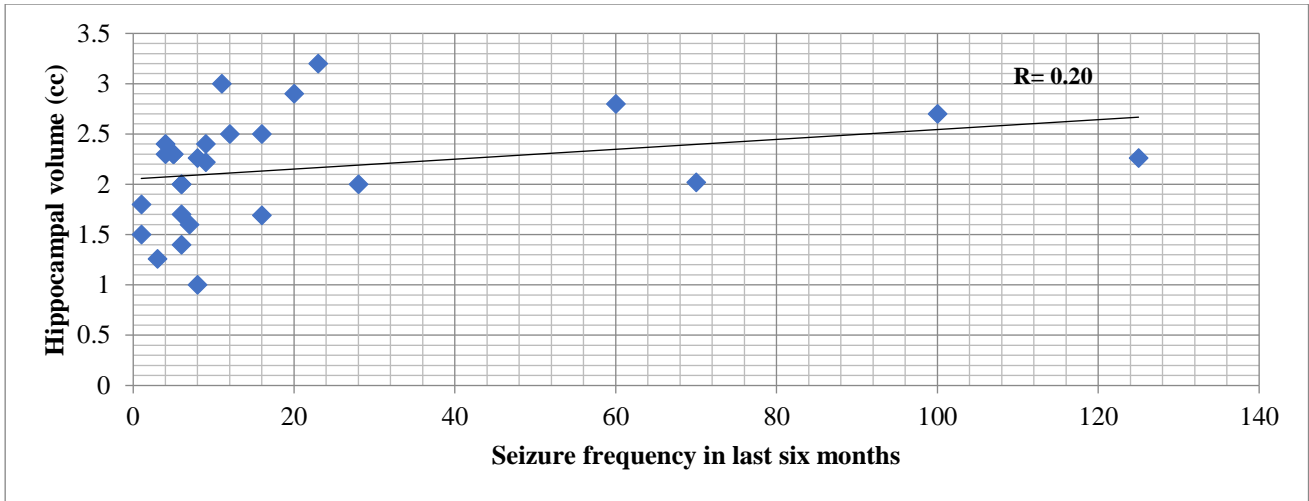


Figure 8: Correlation between seizure frequency (in last 6 months) and manually calculated HV on right side in DRE cases (N=30).

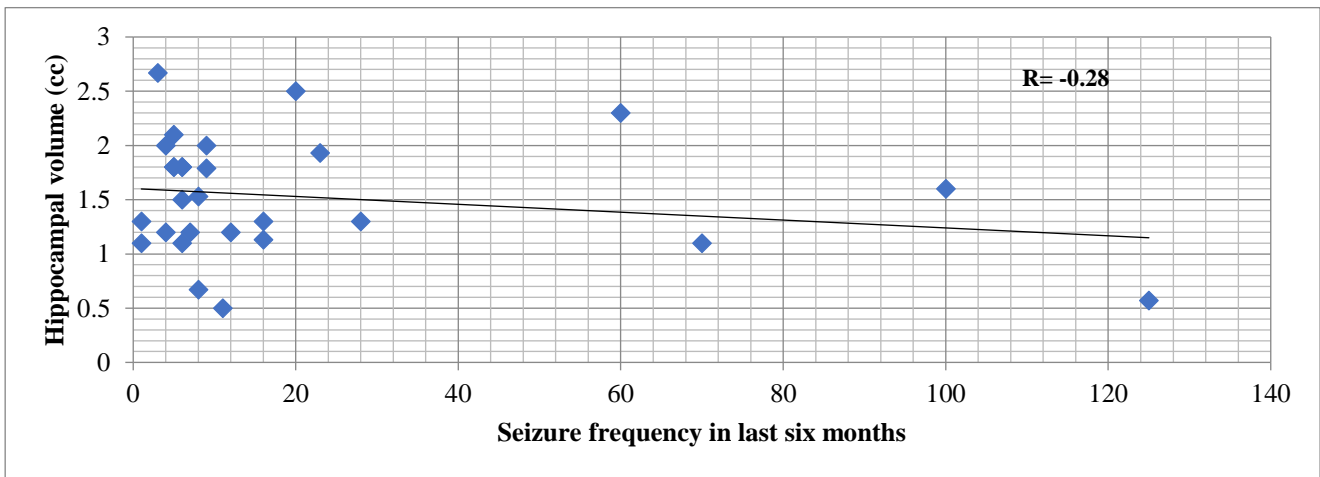


Figure 9: Correlation between seizure frequency (in last 6 months) and manually calculated HV on left side in DRE cases (N=30).

Correlation between duration of epilepsy (in years) and manually calculated HV

Manually calculated hippocampal volume on right side in cases was found to be negatively correlated with duration of epilepsy (Pearson’s coefficient $r = -0.21$). This was not significant at $p=0.01$ level (Figure 6).

Manually calculated hippocampal volume on left side in cases was found to be negatively correlated with duration of epilepsy (Pearson’s coefficient $r = -0.28$). This was not significant at $p=0.01$ level (Figure 7). Correlation between seizure frequency (in last 6 months) and manually calculated HV.

Manually calculated hippocampal volume on right side in cases was found to be positively correlated with

frequency of seizures in last 6 months (Pearson’s coefficient $r = 0.20$). This was not significant at $p=0.01$ level (Figure 8).

Manually calculated hippocampal volume on left side in cases was found to be negatively correlated with frequency of seizures in last 6 months (Pearson’s coefficient $r = -0.28$). This was not significant at $p=0.01$ level (Figure 9).

DISCUSSION

The volumetric measurements of hippocampus are very useful in patients with epilepsy for quantifying hippocampal atrophy, thus providing independent source of information on seizure lateralization, expected postoperative outcome, and aiding in appropriately

selecting patients for invasive preoperative monitoring studies.⁸ A variety of manual and automatic techniques have been used for measurements. Although automatic method is faster and less likely to be affected by rater bias, manual measurements are considered gold standards.¹⁰ There are least chances of inter-observer variations in volume measurements and the method is highly reliable and it can enhance the value of visual analysis of medial temporal lobes.

In our study, 46.6% DRE patients had reduced hippocampal volumes which is close to the volume loss reported by previous studies¹. We had increment in detection of HA from 30% to 46.6% i.e. 16.6% when we used manual hippocampal volumetry in addition to the visual assessment method. This finding is similar to study done by Farid et al who reported 12% increment using quantitative analysis.⁵ Coan et al evaluated 203 patients on 3T MRI and they found that quantification of hippocampal volume and signal can increase the detection of MTS in 28% of patients with mesial temporal lobe epilepsy.¹¹ The increment in our study was seen due to bilateral hippocampal atrophy (13.3%) which was detected only on MHV and not appreciable on visual assessment. Since none of the bilateral HA cases were detected visually, we concluded that hippocampal volumetry is a better tool to detect bilateral HA, a similarity shared with previous studies.^{5,8} Hence quantitative MR imaging may enhance standard visual analysis in temporal lobe epilepsy, providing a useful and viable means for translating volumetric analysis into clinical practice.⁵

Patients of DRE in our study have smaller hippocampal volumes compared to healthy controls with greater volume loss on left side compared to right. The left HV loss (44.3%) was almost double the right HV loss (21.6%) among DRE cases, however there was no statistically significant difference between right and left hippocampi on Schelten's MTA score. Thus, manual hippocampal volumetry is a better tool to pick up hippocampal atrophy.

On correlation between manually calculated hippocampal volume and duration of epilepsy we found that hippocampal volumes of both sides were negatively correlated. Paramdeep et al did not have similar correlation since they had not taken frequency of seizure into account.⁶ However, the majority of previous cross-sectional studies have inferred that more severe hippocampal damage is associated with a longer duration of epilepsy.

Correlation between seizure frequency in last 6 months and manually calculated hippocampal volume was also analysed in our study. Manually calculated hippocampal volume on right side was found to be positively correlated with frequency of seizures in last 6 months (Pearson's coefficient $r=0.20$) however on left side they were found to be negatively correlated (Pearson's

coefficient $r=-0.28$). Both findings were not significant at $p=0.01$ level. Furest et al, found that patients with continuing seizures had decline in hippocampal volume that correlated well with seizure frequency.¹² The majority of previous cross-sectional studies have inferred that more severe hippocampal damage is associated with a greater number of seizures. Longitudinal studies are necessary to ascribe this cause and effect.

CONCLUSION

Thus the ability of MHV to predict the presence and laterality of hippocampal atrophy plays an integral role in evaluation of patients with DRE and should be utilized on a regular basis in clinical practice as it is superior than visual analysis in detecting HA, which can help in guiding surgical resections.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Sachdev N, Gupta S, Singh Y. Role of hippocampal volumetry in drug resistant epilepsy. *Int J Res Med Sci* 2019;7:3077-84.