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KEYWORDS: Focal onset seizure with impaired awareness; Complex partial seizures; Mesial temporal lobe epilepsy (MTLE); Hippocampal sclerosis (HS); Hippocampal Volumetry.

HIPPOCAMPAL MAGNETIC RESONANCE IMAGING IN FOCAL ONSET SEIZURE WITH IMPAIRED AWARENESS -DESCRIPTIVE STUDY FROM TERTIARY CARE CENTRE IN SOUTHERN PART OF INDIA

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Aleena Elizabeth Andrews Resident ,department Of Radiodiagnosis Government Medical College Thrissur

Naufal Perumpalath Associate Professor, Department Of Radiodiagnosis, Government Medical College Kozhikode

Juvaina Puthiyakam Assistant Professor, Department Of Radiodiagnosis, Government Medical College Kozhikode

Andrews MA* Professor Of Medicine, Government Medical College Thrissur. *Corresponding Author E-mail – anjulioness@gmail.com

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ABSTRACT:

Temporal lobe epilepsy is the most common type of focal onset seizure. Focal onset seizure with impaired awareness ,previously known as complex partial seizure (CPS) ,account for 18 - 40% of all seizure types. Hippocampal sclerosis (HS)is the most common cause of temporal lobe epilepsy, which produce focal onset seizure with impaired awareness. It may be detected in MRI visually, but bilateral abnormalities are better identified using volumetric analysis.

AIM:

To assess hippocampus visually and volumetrically in Focal onset seizure with impaired awareness

Settings and Design:

This cross-sectional study includes clinically diagnosed cases of focal onset seizure with impaired awareness undergoing MRI at Government Medical College Calicut.

METHODS AND MATERIALS:

All the subjects (n=56) with clinical diagnosis of Focal onset seizure with impaired awareness were included in the study. (sample size required 42)

STATISTICAL ANALYSIS:

Quantitative variables are reported as means+/-SD and the qualitative variables as percentage. Student's t test used to compare means and correlation coefficient to find relationship between duration of complex partial seizure and hippocampal volume. The values below 5% (p value < 0.05) were considered statistically significant.

RESULTS:

Out of 53 patients studied, hippocampal atrophy was identified visually in 13(24.5%) on right side, 9 (16.98%) on left side and in 6(11.32%) bilaterally. However, with volumetry hippocampal atrophy (not taking T2 signal change) was detected in 15 (28.30 %) on right side ,10(18.86%) on left side and in 7(13.20 %) bilaterally. Hippocampal volumes between ipsilateral and contralateral seizure focus were found to have no significant difference (p-0.84).

CONCLUSIONS:

Visual analysis though efficient in the diagnosis of pathology, MR volumetry may be used as an expert eye in cases of subtle volume loss.

INTRODUCTION:

Epilepsy is characterized by tendency to have recurrent seizures (1) with prevalence of 0.5 - 1%. Focal onset seizure with impaired awareness account for 18 - 40% of seizure types (2).Focal onset seizure with impaired awareness can be of temporal and extra-temporal origin. The commonest form of temporal lobe epilepsy (TLE) is mesial temporal sclerosis where the pathology lies in hippocampus. TLE is responsible for two third cases of intractable epilepsy which is managed neuro surgically. Most of the patients have good outcomes after surgery, and this depends on the evaluation by EEG and magnetic resonance imaging (MRI). Hippocampal sclerosis (HS) can be detected by visual inspection in most cases, however volumetry can assist visual inspection if (3) volume loss is subtle or bilateral resulting in lack of asymmetry, when head is tilted while positioning in gantry or centres lack an expert in epilepsy imaging.

Many MR imaging studies interpreted as normal, was later found to have hippocampal atrophy (HA) at tertiary epilepsy program. There is a strong association between hippocampal asymmetry, identified by quantitative MR imaging, and visual inspection of the volumetric MR studies by two neuroradiologists who are trained to detect HA (91%–97%). Thus, volumetric MR imaging can serve as an expert "eye".

The mean volume of hippocampus is significantly smaller as compared to Western Population as well as Northern Regions of India, suggesting demographic variation in the hippocampal volume. Very few data exist regarding the role of Qualitative and Quantitative Hippocampal Magnetic Resonance Imaging Assessment in Complex Partial Seizures from southern parts of the country.

Patients and Method

STUDY DESIGN AND DATA

This cross-sectional study was conducted among all clinically diagnosed cases of Focal onset seizure with impaired awareness, referred for MRI brain with seizure protocol in 2500 bedded tertiary care hospital from Southern India for a duration of 18 months from February 2018 to August 2019. The study included eligible cases diagnosed by senior neurologist using semiological and EEG criteria as per ILAE 2017 guidelines. The study was approved by the Institutional Review Board of Government Medical College Kozhikode (Calicut) . The written consent was waived by the ethics committee.

MR imaging was performed on 1.5T MRI scanner (Wipro GE) T1W, T2W, diffusion-weighted, and GRE sequences was obtained in axial plane with 5 mm slice thickness and 30% interslice gap. For dedicated hippocampal study, 3D T1w FSPGR(fast spoiled gradient

echo sequence; inversion recovery prep) oblique coronal images (*TE: 5.8, TR: 12.9, FOV: 180mm, slice thickness: 3 mm without interslice gap, matrix 288 x 128 {FE XPE }, NEX -0.75,phase FOV 1,prep time 400 ms ,flip angle 20 ,Bandwidth of 15.63)*, T2W FLAIR coronal oblique images (TE: 95, TR: 8000, FOV: 160 mm, slice thickness: 3 mm) and oblique coronal T2W images (TR: 3700, TE: 97, FOV: 160, slice thickness: 6 mm) covering the whole brain was acquired. Oblique coronal plane was perpendicular to the long axis of hippocampus.

Visually hippocampus was assessed in T2w images for size and signal intensity. All MRIs were assessed for regional atrophy independently by 2 radiologists, blinded to all clinical details except age. The two radiologists had almost perfect agreement on evaluation of hippocampal atrophy visually ($\kappa = 0.8373$).

Volume of hippocampus was obtained from oblique coronal 3D T1w FSGR sequences. Cross-sectional areas of both the hippocampi were measured in these oblique coronal sections by tracing hippocampal boundary manually from hippocampal head to tail. On MRI anterior most boundary of hippocampal head area is taken when the CSF in the uncal recess of the temporal horn was visible and is considered as the most reliable boundary between the hippocampal head and the amygdala. If uncal recess was not visible, then the alveus was used. To standardize the measurement, first section of the anterior hippocampus was defined as point where the uncal recess or alveus first appears. Posterior margin of hippocampal volumetric measurement was defined by MR image where crus of fornix was seen in full profile. Lateral and medial borders were defined as CSF in temporal horn of lateral ventricle and CSF in uncal / ambient cisterns, respectively. Inferior border was defined by grey-white matter junction between subiculum and white matter of parahippocampal gyrus. The volumes of both hippocampi were calculated by summing each of the cross-sectional volumes {cross sectional area × (section thickness + interslice gap)}. As per study conducted by Mohandas, Aravind Narayan et al. on normative data of Hippocampal volumetry Indian population a mean hippocampal volume was found to be 2.411 cm^3 (4).This was much smaller as compared to the data available from the western population.

STATISTICAL ANALYSIS

Statistical analysis was performed using percentages and proportions for qualitative data (visual assessment of hippocampal volume). Quantitative data (volumetry and T2 relaxometry of hippocampus) are presented as mean with standard deviation. The statistical significance of differences in mean volumes between right and left sides were assessed using the '*t' test*.

Values that are 2 SD below the mean of normal; and left–right asymmetries, at least 2 SD above or below the mean of normal are taken as abnormal for individual patients.

All analysis was done using epi info 7 version software and Microsoft excel. Pearson's correlation coefficient and t-test were used wherever indicated. p value < 0.05 was considered to be significant.

Initially visual assessment of the sections of brain was performed, in which those cases without space occupying lesions / perilesional edema involving hippocampus (n= 53) were assessed visually and subjected to volumetry using specific sequences (oblique coronal T2 FLAIR, oblique coronal three-dimensional T1w FSPGR).

RESULTS

There were 56 patients in the study with a mean age of 26.44 with SD 14.78 years. By the Shapiro-Wilk Test of normality, it was found that the data differed significantly from normal distribution (Test statistic 0.856; df 56; p-value is 0.000).

Febrile seizures were the only predisposing factor present among the subjects studied (n-19; 33.93%). None had history of trauma, neonatal convulsions, stroke encephalitis or meningitis in the past. Age, gender and febrile seizure distribution is depicted in table 1.

56 patients with TLE were further divided into right TLE and left TLE groups based on side of EEG localization. Six patients (10.71%) whose seizure foci were either outside the temporal lobe or had a multifocal origin or could not be localized were grouped as extratemporal/unclassified (ET/UC).

Tables

Table 1: Age, Gender and presence of febrile seizures in patients with Complex Partial Seizure

Gender	Number	Median Age with SD	Febrile Seizure
Male	30(53.57%)	22(15.99)	13(43.33%)
Female	26(46.43%)	19.5(13.40)	6(23.36%)

***SD-standard deviation**

MRI in Focal onset seizure with impaired awareness

Out of 56 patients evaluated with MRI, 24 (42.85%) had abnormalities in neuroimaging in the form of tumours, non-specific white matter signal intensity, hippocampal sclerosis and hippocampal atrophy.

HIPPOCAMPUS ON VISUAL INSPECTION

Atrophy

Visual analysis of hippocampus was done only in 53 (94.64%) patients, as three cases had had tumour / perilesional oedema extending into the hippocampus.

Using visual assessment, atrophy with T2 hyperintensity of hippocampus was seen in 9 (16.98%) on right side, 5 on left side (9.4 %) and bilaterally in 1(1.9%) only (table 2).

T2 Hyperintensity of hippocampus

Hippocampal atrophy with T2 hyperintensity suggestive of sclerosis was seen in 9 (16.98%) on right side, however there was a single case of T2 hyperintensity without atrophy. (table 2)

Secondary signs in hippocampal atrophy

In our study out of 53 cases ,13 cases (24.5 %) showed atrophy of mamillary bodies/ fornix with temporal horn dilation ipsilateral to the side of hippocampal atrophy. In the cases where there was bilateral hippocampal atrophy, it was seen that there was atrophy of either mamillary body or fornix and temporal horn dilation visually in both sides.

Table 2: Hippocampal atrophy and T2 hyperintensity distribution in CPS

	Right	Left	Bilateral
Atrophy	13(24.53%)	9(16.98%)	6(11.32%)
T2 hyperintensity	10(18.87%)	6(11.32%)	1(1.9%)
Atrophy with T2 hyperintensity	9(16.98%)	5(9.4%)	1(1.9%)
T2 hyperintensity without atrophy	1(1.9%)	0	0

HIPPOCAMPAL VOLUMETRIC (Quantitative) ANALYSIS

To label hippocampal atrophy a cut off value of 2.4 cc was taken.

Among the 53 cases ,15 (28.30%) had right sided atrophy quantitatively (not taking T2 hyperintensity into consideration), 10 (18.87%) had left sided atrophy and 7 (13.20%) had bilateral atrophy. Combining hippocampal atrophy with signal alteration in T2, 7 had right hippocampal sclerosis ,4 had left hippocampal sclerosis and 2 had bilateral hippocampal sclerosis (see fig 2)

COMPARISONS OF RIGHT AND LEFT HIPPOCAMPAL VOLUMES

Comparisons of right and left hippocampal volumes on ipsilateral and contralateral to seizure focus revealed no significant difference (n=53, mean volume right-2.54, left 2.56 p-0.80).

T2 RELAXOMETRY

Comparing the T2 relaxometry of hippocampus in presumed normal cases and those with hippocampal sclerosis on either side showed statistically significant difference (table 3).

Table 3: Mean T2 relaxometry of hippocampal sclerosis in comparison with normal hippocampus in patients with CPS

Side	Normal	Hippocampal sclerosis	p value
Right	71.32	81.44	0.008(t-2.482)
Left	76.13	86	0.048(t-1.725)

Comparisons of right and left hippocampal T2 relaxometry values ipsilateral and contralateral to seizure focus were analysed, and found to have no statistically significant difference (n=53, mean 81.44 on right ,86 on left and p-0.86).

DISCUSSION:

As per estimate 1 % of world population suffers from epilepsy, of which the most common adult type is Focal onset seizure with impaired awareness (previously known as complex partial seizure) (5).

In our study of Focal onset seizure with impaired awareness ,13 patients (23.21%) had mesial temporal sclerosis, seven had tumours, one had non-specific white matter T2 hyperintensity in extratemporal location, 12 had hippocampal atrophy without signal alteration,1 had T2 hyperintensity of hippocampus without volume loss and 22 (39.28%) had no obvious abnormalities in imaging with 1.5 T MRI. The major tumours detected were glioblastoma multiforme (n 2), dysembryoblastic neuroectodermal tumour (n 3), ganglioglioma (n 1) and glioma (n 1).

Williamson PD, French JA, Thadani VM, Kim JH etal noted that more than 80% cause of TLE is due to Mesial temporal lobe sclerosis (MTS (6). But in our study, 23.21% showed features suggestive of MTS.

As per Muhlhofer W, Tan Y-L, Mueller SG, Knowlton R ,up to 30% of TLE cases have normal ("non lesional" or negative) magnetic resonance imaging (MRI) (7).

Visual assessment of Hippocampus

Magnetic resonance imaging (MRI) features of hippocampal sclerosis (HS) by visual analysis of MRI are described by Cendes et al are Hippocampal atrophy, increased T2/FLAIR signal, loss of internal structure, asymmetry of the horns of the lateral ventricles, atrophy of the anterior temporal lobe and a trophy of the ipsilateral fornix and mammillary bodies (8).

Out of 56 patients, visual assessment of hippocampus was done in 53 patients; three patients with tumours or perilesional oedema extending into region of interest were excluded from the assessment. Increased signal intensity of hippocampus with atrophy visually was found in 13 (24.53%) patients on right side and 9(16.98%) in patients on left side. 6 out of 53 cases had bilateral hippocampal atrophy without corresponding increase in signal intensity in T2.

Atrophy is the most specific and reliable feature of hippocampal sclerosis (HS)(9).

The significance of extent of atrophy of hippocampus becomes important in assessing the prognosis after surgery for mesial temporal sclerosis. In a study by Kim y et al, it was seen that an MR imaging finding of hippocampal atrophy is the most useful sole prognostic indicator(9).

Visual identification of abnormal hippocampus is straight forward if one side is clearly normal and other is abnormal. In symmetric bilateral disease or mild unilateral disease visual analysis may produce problems(8).

The secondary findings in the mamillary bodies and fornix on MR imaging help in the diagnosis and lateralization of MTS(10) . In our study out of 53 cases ,13 cases showed atrophy of mamillary bodies / fornix with temporal horn dilation ipsilateral to the side of hippocampal atrophy.

In patients with subtle findings of unilateral MTS, the secondary imaging features may add to improve diagnostic confidence. Although the secondary MR imaging findings associated with MTS are not sensitive predictors of this entity by themselves, they may offer clues in subtle cases(11).

Hippocampal Volumetry

Quantitative hippocampal volumetry has been shown to predict postsurgical outcome in various studies, however according to Kim y et al the interpretation of MR images by visual inspection alone has a similar prognostic value(9) .In our study, by volumetry, we were able to detect more cases of atrophy quantitatively which was not evident on visual inspection alone. Quantitatively 15 (28.30%) subjects had hippocampal atrophy volumetrically vs 13(24.53%) visually on right side, whereas on left side only 9(16.98%) subjects were detected visually, while 10 (18.87%) were detected volumetrically to have atrophy.

T2 hyperintensity of hippocampus

Another important indicator of hippocampal sclerosis is increased hippocampal T2 signal which indicates gliosis(9). The degree and extent of hippocampal gliosis also correlate with the T2 signal in the hippocampus.
MR imaging studies by Bronen RA et al and Jackson GD et al , have described a variable frequency of T2 signal change in the hippocampus: change was observed in 12% to 65% of patients with hippocampal sclerosis(9)

But in our study, T2 hyperintensity were found in 30.18%. In our study, there is a single case with T2 hyperintensity of hippocampus ipsilateral to the clinical and EEG localisation of the seizure focus (right sided), however with no atrophy.

As per study by Kim y et al and Jack C et al, it has been suggested that finding of hippocampal atrophy is more useful than one of high T2 signal in determining hippocampal sclerosis by histology. As per Kim et al hippocampal atrophy was much more common finding than high T2 signal (97% vs. 61%).

T2 RELAXOMETRY

T_2-weighted hyperintensity is one of the salient radiologic features of HS which can be objectively assessed by quantitative measurement of T2 relaxation (T2 mapping). It has got higher sensitivity over visual analysis. It is of great importance to note that, T2 values may be elevated even in the absence of atrophy(12).Thus, the combination of hippocampal atrophy with an elevated T2 value is both sensitive and specific for HS. As a result , combining findings of hippocampal volumes and T2 values can increase the yield to 99% of visually detected HS but also 28% of those considered visually normal (1).

In our study, comparisons of right and left hippocampal T2 relaxometry values in subjects with normal and abnormal hippocampus were found to have statistically significant difference. Jackson G.D et al performed hippocampal T_2 relaxometry as routine MRI examination and concluded that abnormal T_2 relaxometry is significantly associated with intractable epilepsy (13).

CONCLUSION

The mean volume of hippocampus was significantly smaller as compared to studies available in Western Population as well as Northern Regions of India, suggesting demographic variation in the hippocampal volume. Visual inspection alone may be sufficient to diagnose hippocampal sclerosis, but in cases with subtle volume loss or bilateral atrophy, volumetry serves as an expert eye. Secondary signs such as atrophy of mamillary body, fornix and prominence of temporal horn of lateral ventricle are of paramount significance while assessing the hippocampal atrophy by visually especially if the pathology is bilateral. T2 relaxometry turns out to be a useful tool in detecting hippocampal sclerosis, as striking

difference is noted in cases with hippocampal sclerosis and those presumed to have normal hippocampus.

LIMITATION

1.MTS accounts for majority of the cases of focal onset seizure with impaired awareness(CPS) and hence MRI is done to confirm the diagnosis and as a pre-operative work up. However, since surgery for hippocampal sclerosis is not performed in our institution most of the patients suspected with hippocampal sclerosis are referred to centres where surgery is performed and evaluated with MRI there.
2. Limited sample size.
3. The results of T2 relaxometry is equipment specific and therefore, variations may occur based on the equipment used for evaluation.
4. The study has not considered the frequency of seizure episodes in assessing the hippocampal atrophy.

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