Original Article

Correlation between hippocampal volumes and medial temporal lobe atrophy in patients with Alzheimer's disease

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Abstract

Introduction: Hippocampus undergoes atrophy in patients with Alzheimer's disease (AD). Calculation of hippocampal volumes can be done by a variety of methods using T1-weighted images of magnetic resonance imaging (MRI) of the brain. Medial temporal lobes atrophy (MTL) can be rated visually using T1-weighted MRI brain images. The present study was done to see if any correlation existed between hippocampal volumes and visual rating scores of the MTL using Scheltens Visual Rating Method. **Materials and Methods:** We screened 84 subjects presented to the Department of Neurology of a Tertiary Care Hospital and enrolled forty subjects meeting the National Institute of Neurological and Communicative Disorders and Stroke, AD related Disease Association criteria. Selected patients underwent MRI brain and T1-weighted images in a plane perpendicular to long axis of hippocampus were obtained. Hippocampal volumes were calculated manually using a standard protocol. The calculated hippocampal volumes were correlated with Scheltens Visual Rating Method for Rating MTL. A total of 32 cognitively normal age-matched subjects were selected to see the same correlation in the healthy subjects as well. Sensitivity and specificity of both methods was calculated and compared. **Results:** There was an insignificant correlation between the hippocampal volumes and MTL rating scores in cognitively normal elderly ($n = 32$; Pearson Correlation coefficient = 0.16, $P > 0.05$). In the AD Group, there was a moderately strong correlation between measured hippocampal volumes and MTL Rating (Pearson's correlation coefficient = -0.54; $P < 0.05$. There was a moderately strong correlation between hippocampal volume and Mini-Mental Status Examination in the AD group. Manual delineation was superior compared to the visual method ($P < 0.05$). **Conclusions:** Good correlation was present between manual hippocampal volume measurements and MTL scores. Sensitivity and specificity of manual measurement of hippocampus was higher compared to visual rating scores for MTL in patients with AD.

Key Words

Alzheimer's disease, correlation, hippocampus, medial temporal lobe atrophy rating

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Introduction

Hippocampus is a bilateral structure located deep in the temporal lobes and is covered by adjoining cortical areas.[1] This is a plastic and vulnerable structure which gets affected by a variety of stressors and diseases, of which Alzheimer's disease (AD) is the main one. Bilateral atrophy of the hippocampus is noted in AD. Calculation of hippocampal volumes can be done by a variety of methods, e.g., Voxel-based morphometry and manual delineation.[2] Visual rating of medial temporal lobes is taken to be the surrogate radiological marker for the detailed hippocampal

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volumetry and can be rated visually by standardized rating scale, e.g., Scheltens Visual Rating Scale for medial temporal lobe atrophy (MTL).

Scheltens Scale for MTL is a five-point scale of hippocampal atrophy (normal = 0, severe atrophy = 4) which assesses visually the width of the choroidal fissure, width of the temporal horn, and the height of the hippocampal formation, using the best slice that depicts both hippocampal formations, usually at the anterior pons. This method has shown good inter-rater and intra-rater reliability and has been validated against both linear and volumetric measures using different magnetic resonance imaging (MRI) sequences.[2]

The role of hippocampal volumetry is growing in diagnosis, prognostication, to predict conversion from mild cognitive impairment (MCI) to AD, and also in clinical trials to evaluate newer drugs. However, in a busy clinical setting, the role of hippocampal volumetry is limited. In such a scenario, it is much easier to use Scheltens Visual Rating Method for MTL. This simple scale has been used in India[2,3] and is a quick method of characterization of medial temporal lobes.[4] Also, the data on hippocampal volumes are known in children,[5] young[6] and older adults[7] in India now. Hippocampal volumetry is useful in discriminating not only cognitively normal individuals from those with dementia[8] but can also differentiate MCI[9-12] from various types of dementias.[13-16] Visual rating of medial temporal lobes has been shown to have good sensitivity and specificity in the diagnostic evaluation in a preliminary study of Asian patients.[17]

No study in India, to our knowledge, has correlated or compared the hippocampal volumetry and medial temporal lobe visual rating scale scores to see the agreement between these two. The present study was therefore done to see the comparison of two methods to know superiority of one over the other in the diagnostic assessment of the AD.

Materials and Methods

Screening

We screened 84 subjects presented to the Department of Neurology of a Tertiary Care Hospital with memory/cognitive complaints during the study period (from July 2012 to December 2015) and enrolled 40 subjects. Those who met the diagnostic Criteria for diagnosis of Dementia of Alzheimer's Type (National Institute of Neurological and Communicative Disorders and Stroke, AD-related Disease Association [NINCDS-ARDA] criteria) were recruited for the present study.

Patient selection and diagnostic evaluation

Patients who reported to the Department of Neurology were selected randomly and asked to attend a specialized memory clinic for detailed neuropsychological, radiological, and neurological examination for the diagnosis of AD. A detailed general physical examination was done in all cases to rule out systemic diseases that could have accounted for the diagnosis of dementias other than AD. Routine laboratory examinations and workup for excluding other dementias were done in all cases. Those who met NINCDS-ARDA criteria were recruited for the present study. The selected cases underwent MRI of the brain, and their hippocampal volumes were calculated as per the standard protocol detailed below.

Healthy controls

A total of 32 healthy cognitively normal older adults (M: F = 20:12; mean age = 68.56 ± 1.5 years) were recruited from the staff worker strength of a Tertiary Care Institute. Demographic details such as age, sex, and educational background were noted. Healthy controls were subjected to MRI of the brain using the protocol detailed below in the same manner as cases. A written and informed consent was taken from all study participants. The study was approved by the Institutional Ethics Committee.

Study design

This is a case control study in which hippocampal volumes of patients with AD have been compared with those who are cognitively normal and correlation has been studied with MTL rating scale scores using a standardized scale (Scheltens Visual Rating of MTL).

Scales

1. Mini-Mental Status Examination (MMSE)[16] was used to screen the patient with memory/cognitive complaints and divide them into mild moderate and severe category
2. Scheltens Visual Rating of MTL Rating[2] [Table 1]: A visual rating of medial temporal lobe was done using Scheltens Visual Rating Scale. This was done using T1-weighted coronal section image on MRI brain hard copies. This clinical rating does not require any special radiological training and can be done easily using hard copies of T1-weighted coronal sections of MRI brain. The neuroradiological scale has a good diagnostic accuracy in diagnosing dementia of Alzheimer's type. Table 1 describes the scoring method in detail.

Radiology protocol[7]

Volumes have been calculated using region of interest (ROI) approach, using manual segmentation, three-dimensional, magnetized prepared rapid acquisition gradient echo sequences (3D-MPRAGE) obtained in coronal oblique planes, perpendicular to long axis of the hippocampus [Figures 1 and 2]. The pseudo-images of hippocampus generated using image J by manually outlining of concerned regions are given in Figure 3.

Volumes have been calculated using ROI approach, using manual segmentation-MPRAGE sequences, coronal oblique, perpendicular to long axis of hippocampus.

Table 1: Scheltens visual rating for medial temporal lobe atrophy rating

Scoring	Interpretation
0	No atrophy
1	Minimal atrophy
2	Mild atrophy
3	Moderate atrophy
4	Severe atrophy

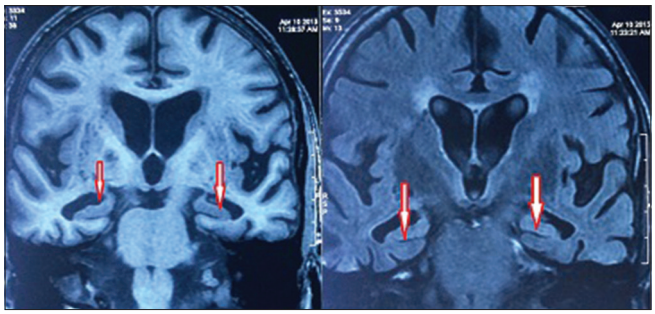

Figure 1: Medial temporal lobe atrophy of a 70-year-old male showing T1-weighted images with diffuse cortical, atrophy particularly marked over the medial temporal and perisylvian areas. Red arrow indicates the atrophy of medial temporal areas, e.g., hippocampal, entorhinal, and parahippocampal areas

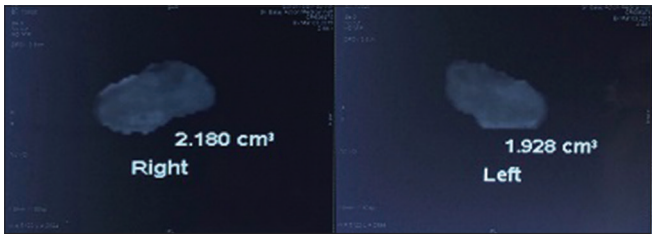

Figure 2: Hippocampus of a 78-year-old women with early Alzheimer's disease showing bilateral volume loss compared to the cognitively normal healthy elderly (Mean hippocampal volume = 2.77 ± 0.6 on the right and 2.73 ± 0.5 cm³)

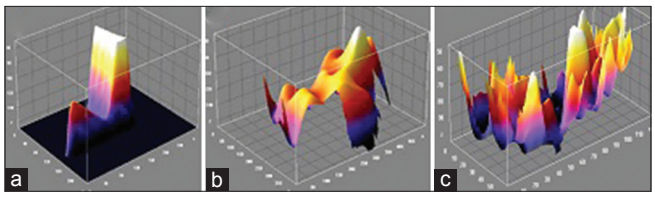

Figure 3: Representative three-dimensional outlines of hippocampal areas done on magnetic resonance imaging brain of the subjects and patients from the current study (Pseudoimages generated by ImageJ, National Institute of Health, USA, downloaded free by http://www.imagej.nih.gov/ij. (a-c) have been drawn to show comparison of normal hippocampus (a) in healthy individuals with those with Alzheimer's disease (b). (c) Represents the manually drawn outlines of right medial temporal lobe for comparison

In the current study, hippocampal volume has been measured using 1.5 Tesla Magnetic Resonance (Magnetom Symphony 1.5 Tesla Scanner, Germany). Images were acquired in T1, T2, fluid attenuation inversion recovery sequences in axial, coronal and sagittal planes. A T2 sagittal section was used to plan the sequences (MPRAGE) for the estimation of hippocampal volumes.

Images perpendicular to long axis of hippocampus, oblique coronal section were taken for delineation of the selected area (ROI). T1-weighted coronal images were used in all slides wherever hippocampus was visible. Image parameters were as follows: a 3D image reconstruction was done, using fast low angle shoot. Slice thickness was 1 mm with a repetition time of 14 s (total scan time = 5.22 min). Hippocampus was defined as Coruna Ammonis, dentate gyrus, and subiculum. Hippocampus is delineated using the following anatomical landmarks.

In the first slide of T1-weighted MRI images of the brain, where the hippocampus is first visualized and the the area bordering amygdale was considered to be the most anterior part of hippocampus. Alveus was used as a landmark to separate amygdale from hippocampus. Precaution was taken not to include part/s of amygdale. 3D viewing images were used to clearly define hippocampal boundaries.

Alevus was visualized as a band of white matter and used as the border between hippocampus and amygdale. Hippocampal volume was calculated by summing up the area that has been delineated using the manual cursor. Area thus obtained is multiplied by 0.15 (1 mm slice thickness and 0.5 mm inter-slice gap). This gives values in cubic centimeters.[7]

Image processing

All image processing steps were performed as per the standard protocol.[7] The 3D MRI data were interpolated in the slice-select dimension to give cubic voxels, and interpolated in plane to the equivalent of a 512 × 512 matrix. 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.

On a 2D plane, hippocampal anatomic boundaries were defined to include the CA1 to CA4 sectors of the hippocampus proper, the dentate gyrus, and the subiculum. Manual delineation of all the parts mentioned was done in all slices wherever visible. The posterior boundary of the hippocampus was determined by the oblique coronal section in which the crura of the fornices were identified in the full profile.

Statistical analysis

The 21st version of Statistical Package for Social Sciences (SPSS®-SPSS Inc., Chicago, IL, USA) was used for data analysis. Normality of data was checked using Q-Q plot. Correlation and regression were performed. Differences between left and right hippocampal volumes were compared using paired *t*-tests. Cohen's Kappa was used to estimate inter-rater reliability. Two-sided $P < 0.05$ was used to test level of significance.

Results

Out of 84 patients screened, 40 (M: F = 28:12; 62.36 ± 1.2 years; mean MMSE = 17.12 ± 1.2, duration of illness = 3.2 ± 1.2 years) met the NINCDS-ARDA diagnostic criteria for AD. The hippocampal volume values of the patients were checked for the normal distribution using Q-Q plot [Figure 4]. Correlations between age and hippocampal volumes were not significant (Pearson's correlation coefficient [r] = −0.29; $P > 0.05$) in both groups (cognitively normal and those with AD). Detailed results are presented in Table 2.

There was an insignificant correlation between the hippocampal volumes and MTL rating in cognitively normal elderly (n = 32) (Pearson's correlation coefficient = [r] =0.16; $P > 0.05$). Also, the left and right hippocampal volumes were not

significantly different ($P > 0.05$). There was a moderately strong correlation between hippocampal volume and MMSE in the AD group (Pearson's correlation coefficient [r] =0.60; $P < 0.05$).

Sensitivity and specificity analysis of hippocampal volumes measurements in detecting dementia of Alzheimer's type was done. The sensitivity of the hippocampal volumetry is high (92%; 95% confidence interval = 68.30%–98.77%). The specificity of the test was relatively lower (84%; 95% confidence interval = 22.28%–95.67%). Sensitivity and specificity of MTL, as rated by Scheltens Visual Rating Method, was low (sensitivity = 66.67%; 95% confidence interval = 40.99%–86.66%). The specificity was 57.14% (95% confidence interval = 28.86%–82.34%). A comparison of both modalities using Pearson Chi-square showed that both were statistically different showing manual measurements had a greater sensitivity and specificity compared to the visual inspection ($P = 0.05$; 95% confidence interval = −16.4169–45.4016; degree of freedom = 1).

Correlation between manually measured hippocampal volume and MTL atrophy rating as obtained by Scheltens Visual Rating Method for medial temporal lobe in patients with AD was moderately strong (Pearson's correlation coefficient [r] = −0.54; $P < 0.05$; Figure 5). Correlations in the healthy subjects were mild and insignificant (Pearson's correlation coefficient [r] = 0.16; $P > 0.05$).

Left and right hippocampal volumes analysis of patients with AD ($n = 40$) was done using unpaired t-test. Both groups did not have any statistical difference; two-tailed P value was not significant (0.1409). In MTL rating, the inter-rater agreement was high (Cohen's Kappa = 0.63). Regression analysis between the mean hippocampal volumes (left and right) and the MTL was done; coefficient of determination (r^2) was found to be 0.62.

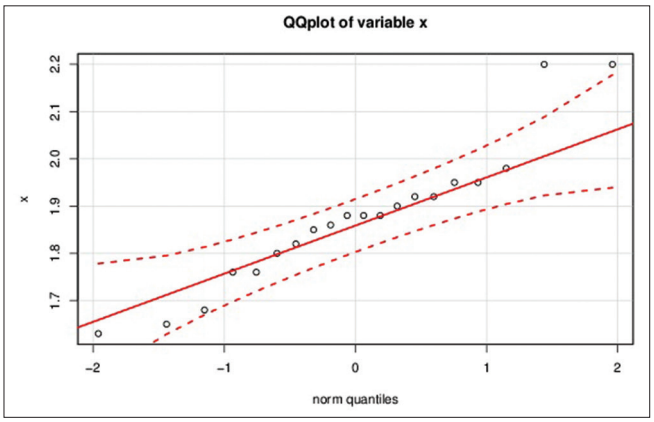

Figure 4: Q-Q plot of hippocampal volumes of patients with Alzheimer's disease to check normalcy of data (*x* variable). The data are normally distributed. Centering of the data around the mid-line indicates that the data are normally distributed

Discussion

Hippocampal volume has received attention in the diagnostic and prognostic evaluation of neurocognitive disorders.[1] This has also been used in research setting[4] where it has been shown to differentiate cognitively normal elderly from those with AD,[5] monitor progress to treatment in patients with AD and MCI, differentiate MCI to AD based upon volumetric data. Longitudinal results confirm that initial hippocampal volume is predictive of conversion to AD[6] and can also differentiate AD from MCI.[7] It can also differentiate dementia from pseudodementia[8] and different types of dementias can also be differentiated in combination with clinical and other supportive laboratory data.[9] Pseudodementia is a depressive syndrome seen in older people in which they exhibit symptoms consistent with dementia but the cause is actually depression.

A variety of manual and automatic techniques have been used for measurements.[10,11] Although automatic method is faster and less likely to be affected by rater bias, manual measurements are considered gold standards.[12]

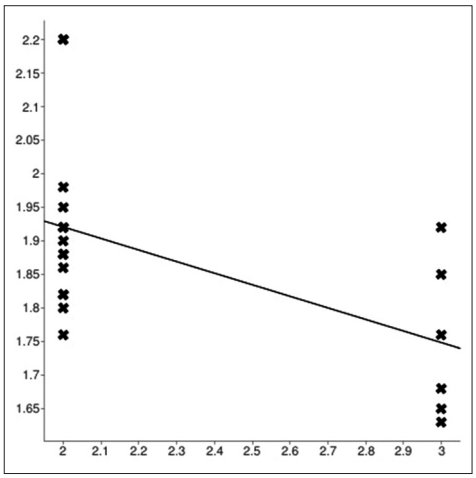

Figure 5: Correlation between manually measured hippocampal volume and medial temporal lobe atrophy rating obtained by Scheltens Visual Rating Method for medial temporal lobe. Pearson's correlation coefficient (*r*) was –0.54. The coefficient value was in minus indicating, when one MTL (*x*) was low, the other value-hippocampal volume (*y*) also was lower. This indicates a good deal of agreement between two methods

Table 2: Left and right hippocampal volumes, Scheltens medial temporal lobe atrophy rating, and correlations between the two in Alzheimer's disease patients and healthy controls[a]

	HV		MTL[b]		Correlation between MTL and HV	*P*[c]	Pearson's Chi-square test[d]
	Left	Right	Left	Right			
AD	1.82±0.1	1.87±0.14	2	2	−0.54	<0.05	<0.05
Healthy	2.62±0.4	2.72±0.4	1	1	0.16	>0.05	>0.05

[a]Values of hippocampal volumes are expressed in cm^3, [b]Values of medial temporal lobe atrophy rating scores are expressed as modes, [c]Values <0.05 were considered statistically significant, [d]Test of proportion was used to know the significant difference between proportions. AD = Alzheimer's disease, HV = Hippocampal volume, MTL = Medial temporal lobe atrophy

MTL is the hallmark of patients with AD and is also seen in MCI and in few other dementias. It can also differentiate dementia from pseudodementia, MCI from AD and is a good diagnostic aid in the diagnosis of AD. It can be done promptly in a busy clinic without the need of complicated MRI setup needed for volumetry.[2] Also, volumetry is a time-consuming business and needs good deal of training in radiology and neuroanatomy to measure hippocampal volumes. However, it is considered to be gold standard in the diagnostic evaluation of disorders involving hippocampus, e.g., epilepsy or dementia.

The present study reports correlation between hippocampal volumes measured by manual delineation and MTL as assessed by Visual Rating of MTL using Scheltens Rating Scores. A moderately strong correlation was found between the two with significant *P* value in patients with AD. In healthy controls, however, no significant correlation was obtained. Our results are in agreement with the previously reported findings of the same.[11,14]

Volumes obtained in the present study are not significantly different from the volumes reported earlier from India.[7] Current study reports a decreasing MMSE score correlates with decreasing hippocampal volumes in AD. The same has been demonstrated earlier as well.[18] This supports the notion that decrease in MMSE mean the severity of dementia is more and it has also been correlated with Visual Rating Scale of Scheltens as well.[19]

There are several uses of volumetry: It can help to differentiate dementia from pseudodementia. The extent of volume loss in the latter will be lesser. Likewise, different subtypes of dementias can be differentiated based upon volumetry. The extent of volume loss in the AD is reported to be higher compared to other dementias such as fronto-temporal, normal pressure hydrocephalus, and vascular dementias. Notably, this is one of the common diagnostic confusion in demented patients. Of course the same can be used for clinical trial purposes when a new drug is under evaluation.

There is a reason to believe that those with smaller baseline hippocampal volume are more likely to convert compared to those with larger volumes.[18] So overall, volumetry can enhance diagnostic accuracy of MRI as a diagnostic modality in a significant way. The only impediment is that manually outlining hippocampus in both sides could be tedious and labor-intensive process. However, it should be noted that in patients with AD, since there is a significant shrinkage of hippocampal volume, it takes just 5–15 min for an experienced observer to calculate hippocampal volume on a 1.5 Tesla machine. In those with a large hippocampal volume, since it will be visible in several cuts, it would take longer time. Although automatic segmentation methods are available, manual delineation of hippocampus is still considered to be the gold standard method. The definition of hippocampus has to be proper and one should be cautious not to leave important are and not to include something that is not important, e.g., parahippocampal area, amygdale and choroid plexus.

There have been attempts to compare sensitivity of visual rating of medial temporal lobes and manually calculated hippocampal volumes in cognitively normal, those with MCI and AD using a new scale.[20] To our knowledge, this is the first study done to compare the correlation of these two parameters in AD patients of Indian origin. The results of the present hippocampal volume analysis are in agreement with the studies done by Bhatia *et al*.[21] and Jack *et al*.[18] Results of hippocampal volumes of those who are cognitively normal and those who have AD are in agreement with a similar study from China[19] (n = 102). In this study, the 95% normal values of hippocampal volumes in the young adults ranged from 2.52 to 3.11 cm^3 (right), and from 2.40 to 2.98 cm^3 (left); in those aged ≥60 years, the volumes ranged from 2.33 to 2.65 cm^3 (right) and from 1.98 to 2.64 cm^3 (left). There was no significant difference in the volumes of hippocampal formations between two groups (older and younger adults). However, a decrease of the volumes of hippocampus was seen in those older than 60 years.[19,22] Our results are in agreement with Indian study[6] though methodological differences were there in the manner in which volumetric calculations were done in both studies due to the use of different protocols.[23,24]

A recent large study (n = 544)[25] compared visual assessment of MTL with hippocampal volume in a healthy, non-demented elderly population (age range 60–87 years). Significant correlation (r) = −0.32, $P < 0.001$) was found between hippocampal volume measurements and visual rating of medial temporal lobes. There was a highly significant correlation between volumetric measurements of the hippocampus and MTL scoring. In normal aging, there is an increasing MTL score. For nondemented elderly individuals ≤70 years, an MTL score of 0–1 may be considered normal, compared with MTL ≤2 for 70–80 years and MTL 3 for >80-year-old individuals. This is the only study to our knowledge that has correlated these two common measures. However, it has done so only in healthy individuals while our study has done the same in both healthy and those with a diagnosis of AD.

Medial temporal atrophy rating is quick and easy though manual outlining of hippocampus is considered to be gold standard.[15,26] Combining MMSE scores and visually rated MTL ratings yielded a higher sensitivity for AD, and for other dementias.[27] In the present study, regression analysis between the mean hippocampal volumes (left and right) and the MTL was done. Coefficient of determination (r^2) was found to be 0.62, indicating that to a great deal, the variances in hippocampal volumes were being explained by MTL rating scale scores.

Volumetry is a time-consuming method as discussed previously as there was a 10-fold difference in time spent on rating MTL (1–2 min) versus time spent calculating the medial temporal lobe volume (10–12 min) on a single subject in one study.[28] In a study of 95 participants without dementia (mean age 62 ± 10 years), it was shown that MTL assessment gives a fair idea of hippocampal volumes.[29]

Although the current study has shown good correlation between manually measured hippocampal volumes and MTL rating scores using a standardized scale, it has a few limitations: sex matching of the subjects has not been adequately done due to a well-reported bias of male preponderance of dementia cases in India. In addition, the sample size is not very large. Although studies with small sample size (30) have previously been reported ([AD [n = 21] from age-matched controls [n = 21];[30]

28 patients with AD and 29 healthy controls),[31] these have been done in ageing individuals and their comparison with AD and not in AD patients using standardized scales to the best of our knowledge. Due to small sample size, sensitivity and specificity of medial temporal atrophy ratings is not found to be very high and the same can be repeated using a larger sample size to confirm the results.

The comparison of this rating has been done with neuropsychological ratings too and MTL has been found to be superior.[17] MTL ratings have been shown to discriminate between AD, MCI and those who are cognitively normal. Combination of volumetry and visual assessment increases diagnostic accuracy of medial temporal lobe assessment.[32] More often, reporting of medial temporal lobes atrophy in the clinical settings has been suggested[33] as this is common in aging and in the AD[34] and increases the diagnostic accuracy of AD.[35]

Conclusions

In AD group, there was a correlation between decreasing MMSE scores and hippocampal volumes. Sensitivity and specificity of manual measurement was higher compared to visual method but the latter can be used on outpatient basis in the assessment of AD where the facilities/training for performing detailed volumetric measurements of hippocampus are not available.

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Conflicts of interest
There are no conflicts of interest.

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