Original Article

Evaluation of Early Cerebral Atrophy in Mild Cognitive Impairment with Positive Amyloid PET using MRI Volumetric Measurement

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Objective: To identify early cerebral atrophy by using magnetic resonance imaging (MRI) volumetric measurement to distinguish mild cognitive impairment (MCI) from normal aging.

Materials and Methods: A retrospective study in 29 Alzheimer's disease (AD) patients (mean 75.6±7.3 years), 11 MCI patients (mean 68.8±3.9 years), and 27 healthy control (HC) subjects (mean 69.3±4.7 years) was performed with analysis of neurological and neuropsychiatric test, and underwent 3T MRI with high-resolution 3D-T1W. Quantitative volumetric analysis of brain including surface area, cortical gray matter volume, cortical thickness, and hippocampal subfields was performed by using FreeSurfer software.

Results: The diminishment of cortical gray matter volume and cortical thickness were involved in most of brain regions, predominantly in temporal lobe with statistical significance in AD compared with MCI and HC. Comparison between amyloid positron emission tomography (PET) positive MCI subjects and HC has statistically significant difference in most regions of hippocampal subfield. The highest accuracy of 90.01% with sensitivity of 50% and specificity of 100% were found at subiculum. A comparison between amyloid PET positive MCI subjects and amyloid PET negative MCI subjects revealed significant differences at right molecular layer, right/average GC-ML-DG, right CA2/3, right CA4, and average CA4 with good accuracy, sensitivity, and specificity.

Conclusion: The present study confirmed improved sensitivity of MRI volumetric measurement with hippocampal subfield analysis to identify early stage of AD in MCI patients, at least compared with positive amyloid PET MCI. Study with higher number of subjects using this method to discriminate MCI and normal aging control would provide benefits as the screening tool in older population.

Keywords: Hippocampal subfield; Volumetric analysis; Alzheimer's disease; Mild cognitive impairment

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By 2025, Thailand will be an absolute aging society, which means that more than 20% of the population age will be more than 60 years old[(1)] and health care problems involving older people would be increased. One of these is cognitive impairment or dementia.

Alzheimer's disease (AD) is the most common form of dementia. In 2016, medial temporal atrophy (MTA) was added into diagnostic criteria for probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) guideline. Although, neuroimaging is one of the AD biomarkers, it is still challenging in early detection of the disease before dementia symptoms occur. Due to more accessible and available magnetic resonance imaging (MRI) along with evolution of advanced technology, many studies still pay attention to use the structural MRI (sMRI) as a biomarker for predicting AD in clinical practice.

Previous studies reported increased sensitivity of MTA especially hippocampal volume (HV) measurement in identifying mild cognitive impairment (MCI) patients who would be AD later, the so-called AD-converted MCI (cMCI). Although HV has been reported as being not probably sensitive enough

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to evaluate people with dementia in the previous studies[2-5], development of recent software such as FreeSurfer to measure AD-signature areas and subfield structure of hippocampus has led to more exploring sMRI[6].

The authors' previous study found possibility in using hippocampal subfield volume to identify MCI with positive amyloid positron emission tomography (PET) of brain[7]. In the present study, the authors aimed to explore the possibility to add AD signature areas into hippocampal subfield measurement to improve accuracy of detecting cMCI.

Materials and Methods

The present study was approved by the Ethical Committee Board (COA No. Si137/2015). The present study was done retrospectively in a tertiary hospital and the subjects were recruited between August 2015 and May 2019 including 29 AD patients (mean age 75.6±7.3 years old), 11 MCI patients (mean age 68.8±3.9 years old), and 27 HC subjects (mean age 69.3±4.7 years old) with analyses of neurological and neuropsychiatric tests. The demographic data are shown in Table 1. Sixty-seven subjects were recruited into the analyses.

The patients were diagnosed as AD according to NINCDS-ADRDA for probable AD with the Thai Mental State Examination (TMSE) score less than 26 and the Clinical Dementia Rating (CDR) score equal or more than 0.5. Subjects were excluded from the study if any psychiatric or neurological illness other than AD was present. The criteria for MCI subjects were TMSE scores between 24 and 30, subjective memory complaint with preserved activities of daily living (ADLs), CDR score of 0.5, and absence of dementia according to NINCDS-ADRDA criteria. For healthy control subjects (HC), the criteria were scores between 24 and 30, CDR score of 0, no neurological or psychiatric illness, non-demented, and normal ADLs.

The amyloid PET brain studies were performed with in-house [^{18}F] AV45 PET tracer and scanned with Discovery STE PET/CT scanner (GE Healthcare, WI, USA) with details as in the previous report[8,9]. Each amyloid PET study was interpreted as amyloid positive or amyloid negative in consensus by two experienced nuclear medicine physicians, blinded to clinical information and MRI data, in the same way as in the authors' previous report[7]. Six MCI patients (from total of 11 MCI patients) had positive result of amyloid PET. The authors defined MCI patients who had positive amyloid PET scan as AD-converter MCI.

Table 1. Demographic data of subjects in AD, MCI, and HC groups

	AD (n=29)	MCI (n=11)	HC (n=27)
Sex (female/male)	14/15	3/8	18/9
Age (year); mean±SD (range)	75.6±7.3 (60 to 90)	68.8±3.9 (63 to 74)	69.3±4.8 (62 to 80)
Education (year); mean±SD (range)	9.9±5.4 (3 to 17)	15.4±4.3 (7 to 20)	12.1±5.4 (4 to 20)
TMSE; mean±SD	22±3.7	26.7±1.7	27.8±1.8
CDR; n (%)			
0	0 (0.0)	0 (0.0)	27 (100)
0.5	21 (72.5)	11 (100)	0 (0.0)
1.0	8 (27.5)	0 (0.0)	0 (0.0)

AD=Alzheimer's disease; MCI=mild cognitive impairment; HC=healthy control; TMSE=Thai Mental State Examination; CDR=Clinical Dementia Rating; SD=standard deviation

MRI data

All imaging data were acquired using 3T MR system (Ingenia, Philips Medical System, Best, the Netherlands) with a 32-channel head coil. T1-weighted imaging was performed using a 3D-TFE. The detailed parameters were echo time (TE) 4.8 milliseconds (msec); repetition time (TR) 9.8 msec; matrix size 352×352; field-of-view (FOV) 230×230 mm², the total acquisition time was six minutes four seconds.

Image processing

Structural MRI data were processed with the FreeSurfer software version 6.0 (http://surfer.nmr.mgh.harvard.edu)[10-12] using the "recon-all" processing stream[13] with default parameters to create a 3D cortical surface model[11]. Briefly, the procedure included motion correction, intensity normalization, Talairach registration, skull stripping, segmentation of subcortical white matter (WM), tessellation of the gray matter (GM)/WM boundary automated topology correction, and surface deformation. Finally, the FreeSurfer created a surface 3D model of the cortex using intensity and continuity information.

Cortical analysis

Cortical thickness was calculated as the shortest distance between the GM/WM boundary and pial surface at each vertex across the cortical mantle, measured in millimeters (mm). In addition to vertex-based reconstruction, the FreeSurfer automatically parcellated the cortex into 34 gyral-based regions-of-interest (ROIs) per hemisphere, according to the Desikan-Killiany atlas. For each of the 68 cortical parcellations, the FreeSurfer calculated 1) the average

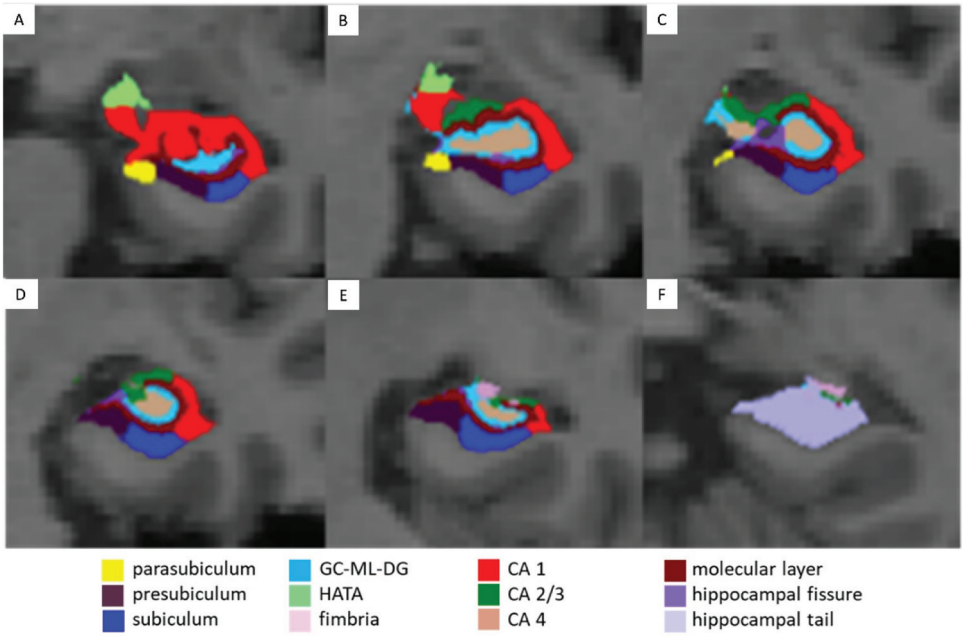

Figure 1. Magnified views of left hippocampal subfields in coronal plane demonstrated from anterior to posterior (A-F).

cortical thickness (in mm), 2) total cortical surface area of the pial (in mm^2), and 3) the cortical GM volume (in mm^3). Each brain regions were defined as the left (Lt), the right (Rt), and the average (Avg) of the left and right.

Hippocampal subfields

Hippocampal subfields were automatically segmented using the FreeSurfer software. The total subfields included the following parts, CA1, CA2/3, CA4, molecular layer, alveus, granule cell layer and molecular layer of dentate gyrus (GC-ML-DG), hippocampus-amygdala-transition-area (HATA), tail, subiculum, pre-subiculum, para-subiculum, and fimbria (Figure 1). The contrast between the subfields CA2 and CA3 could not be distinguished on MRI, thus, they were combined in the present study, and the alveus was removed due to its thin shape and unreliable segmentation[14]. The hippocampal subfield volume was measured in mm^3. Each region of hippocampal subfields was defined as left, right and average of the left and right.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA). The differences among AD, MCI and HC subjects were compared in cortical thickness, surface area, GM volume and hippocampal subfield by using one way ANOVA with Bonferroni post hoc comparison. Comparison between MCI subjects who had positive result of amyloid PET and HC were tested using unpaired t-test. Comparison between amyloid PET positive MCI subjects and amyloid PET negative MCI subjects were also performed with the same method. All results were predetermined as statistically significant when p-value less than 0.05. Statistical evaluation of the diagnostic performance was done by using the receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), sensitivity, specificity, and accuracy were calculated.

Results

Cerebral cortex measurement

Significant decreased cortical thickness involved most of the brain regions in AD as compared with MCI and HC was found ($p<0.001$ to 0.034). There was no significant difference of cortical thickness between MCI group and HC group.

Significantly decreased surface area was found in some area of frontal and temporal lobe in AD compared with HC. No significant difference of surface area was found between MCI and HC or AD and MCI group.

Decreased GM volume was found at temporal lobe in AD compared with MCI except for left inferior temporal region. Few areas of frontal, parietal, occipital, and insula lobes showed significantly

Table 2. Mean of hippocampal subfield volume (mm^3), comparison between PET positive MCI, and HC subjects

	PET positive MCI (n=6); mean±SD	HC (n=27); mean±SD	p-value
Avg hippocampal tail	437.7±103.1	502.5±61.8	0.049
Lt. subiculum	338.9±82.8	406.4±49.0	0.012
Rt. subiculum	354.5±57.5	409.2±46.5	0.018
Avg subiculum	346.7±69.6	407.8±46.7	0.013
Lt. CA1	491.0±59.9	579.3±73.1	0.010
Rt. CA1	529.3±63.1	595.3±69.0	0.040
Avg CA1	510.2±58.4	587.3±69.0	0.016
Lt. molecular layer	433.7±73.1	516.5±58.4	0.005
Rt. molecular layer	465.9±52.2	529.2±54.2	0.014
Avg molecular layer	449.8±61.0	522.9±55.4	0.007
Lt. GC-ML-DG	220.2±31.0	264.7±29.3	0.002
Rt. GC-ML_DG	247.2±21.1	278.1±26.3	0.012
Avg GC-ML-DG	233.7±23.7	271.4±26.7	0.003
Lt. CA4	193.4±29.5	228.3±25.1	0.006
Rt. CA4	214.6±18.7	238.5±22.2	0.020
Avg CA4	204.0±22.8	233.4±22.7	0.007
Lt. fimbria	61.7±18.3	75.7±13.1	0.035
Rt. fimbria	60.3±18.2	74.3±13.7	0.041
Avg fimbria	61.0±18.1	75.0±11.4	0.021
Lt. HATA	47.6±7.9	56.1±7.4	0.017
Avg HATA	50.8±6.3	57.6±6.5	0.028
Lt. whole hippocampus	2676.6±502.5	3137.3±328.2	0.008
Rt. whole hippocampus	2851.2±316.2	3213.7±313.3	0.016

PET=positron emission tomography; MCI=mild cognitive impairment; HC=healthy control; Avg=average; Lt.=left; Rt.=right; CA=cornu ammonis; GC-ML-DG=granule cell layer and molecular layer of dentate gyrus; HATA=hippocampus-amygdala-transition-area; SD=standard deviation

decreased in AD compared with MCI. There was significantly decreased GM volume in all regions of temporal lobe and insula, some areas of frontal, parietal and occipital lobes in AD compared with HC. No significant difference of GM volume was found between MCI group and HC group ($p<0.001$ to 0.045).

Hippocampal subfields

There was significant decreased volume in most regions of hippocampal subfield in AD compared with MCI ($p<0.001$ to 0.046). Significantly decreased nearly all hippocampal subfield volume was also found in AD compared with HC ($p<0.001$ to 0.029). No statistically significant difference between MCI and HC in every region of hippocampal subfield was found.

In a subgroup analysis comparison between amyloid PET positive MCI subjects and HC, there was statistically significant difference in most regions of hippocampal subfield volumes including whole HV (Table 2). The sensitivity, specificity, and accuracy of detection PET positive MCI when compared with HC using specific cut off value were shown in Table 3. The highest accuracy of 90.01% with sensitivity of 50% and specificity of 100% (AUC=76) was found at the subiculum.

Table 3. The sensitivity, specificity, accuracy and 95% CI of detection PET positive MCI as compared with healthy controls with specific hippocampal subfield volume cut off value

Regions	Cut off value (mm^3)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
Subiculum	<315.3	50	100	90.91
CA1	<586.27	100	51.8	60.6
CA4	<225.5	100	70.37	75.76
Fimbria	<64.27	66.67	85.19	81.82
Whole hippocampus	<3142.09	83.33	62.96	66.67

CA=cornu ammonis; CI=confidence interval

For a comparison between amyloid PET positive MCI subjects and amyloid PET negative MCI subjects, the study revealed significant differences at right molecular layer, right and average granule cell and molecular layer of the dentate gyrus (GC-ML-DG), right cornu ammonis (CA) 2/3, right CA4, and average CA4 ($p<0.001$ to 0.03). With a specific cut off value of less than 227.9 mL at right CA4, the present study showed accuracy of 90.9%, sensitivity of 83.3%, and specificity of 100% (AUC=0.97) to detect amyloid PET positive compared to amyloid PET negative MCI.

Discussion

There are no available treatments that completely stop or reverse the progression of AD, which worsens as it progresses, and eventually leads to death. MCI is a transitional disease stage between normal aging and AD. However, people with MCI do not always lead to dementia. They may revert to normal cognition or remain stable[15]. The important issue is to identify MCI patients who convert to AD for disease-modifying treatment. Therefore, identifying those in earlier disease provides benefit. Both sensitivity and specificity are important in this aspect. Too high sensitivity may cause over diagnosis and unnecessary concern over dementia for the patients with no disease. Too high specificity may be under diagnosed early AD and delayed treatment. The authors, therefore, considered accuracy to balance between both.

The pathophysiology of AD is related to the injury and death of neurons, initiating in the basal forebrain especially hippocampus, which is involved with memory and learning, and then atrophy affects the entire brain[16]. Evaluation of hippocampal subfield analysis from sMRI has opened visualization of in vivo destruction from pathological toxic substrate corresponding with Braak's stage II or III. The present study and the others confirmed more sensitivity of hippocampal subfield analysis over AD signature areas in early detection of cMCI[17-19]. A more sensitive diagnostic tool such as amyloid-PET study has been accepted for identifying early stage of the disease especially in MCI[20,21]. In the present study, the authors defined MCI patients having positive amyloid PET scan as AD-converter MCI. Though some discordance of the findings for the specific subfield region, most of the study including the authors' confirmed significant accuracy of subiculum for identifying early cMCI[9,22-25]. Besides, the authors also found difference of subfield volume between MCI with positive and negative amyloid PET study.

Brain volume loss is also displayed in normal aging and MCI. With the concept of AD-continuum, progression of neuronal injury from hippocampus or basal forebrain to neocortex was confirmed by the present study and others[17,26]. Cerebral cortex was significant atrophy in AD subjects compared with normal aging. The affected regions are predominantly in temporal lobe[26]. According to cortical analysis, the authors found no significant difference between MCI and HC group in any regions. This confirmed that, using hippocampal subfield volumetric measurement might be more sensitive to discriminate AD-converter MCI and normal aging. Further longitudinal study of hippocampal subfield volume of MCI patients who developed AD would provide more reliable information.

There were some limitations of the present study especially that there was no follow-up on MCI patients and it was a small sample size. The result of the present study might not be able to use in clinical practice at present. However, with more future studies, sMRI still would be an impressive way for early detection of AD in clinical practice.

Conclusion

The present study confirmed improvement of MRI volumetric measurement with hippocampal subfield analysis for identifying early stage of AD. MR-base volumetric measurement of hippocampal subfield would be the potential diagnostic tool for discriminating amyloid PET status among MCI patients. Study with higher number of subjects using this method to discriminate cMCI and normal aging would provide benefits as the screening tool in elderly population.

What is already known on this topic?

Conventional MRI study can evaluate brain abnormality in people with dementia, however the information is probably not enough in clinic.

What this study adds?

MRI volumetric measurement with hippocampal subfield analysis might add more information to identify early stage of disease of AD in MCI patients and should be correlated with neurological and neuropsychiatric test.

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Conflicts of interest

The authors declare no conflict of interest.

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