Hippocampal Volume and Entorhinal Cortex Thickness in Alzheimer's Disease

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Abstract

Magnetic Resonance Imaging (MRI) is the standard imaging evaluations in Alzheimer's Disease (AD). Information regarding hippocampus and entorhinal cortex sizes plays an important role in Alzheimer's disease. This study aims to determine hippocampal volume and entorhinal cortex thickness in Alzheimer's disease obtained from a group of patients who underwent head MRI.

This study was an observational study with retrospective approach in patients who were diagnosed with AD and had available head MRI examination results. A total of 14 patients were diagnosed by a neurologist with AD using MMSE, Hachinsky, and NIA-AA criteria.

From head MRI measurement in AD patients, we found that the mean volume of right, left, and total hippocampal was 1700±0.395 cm^3; 1.670±0.349 cm^3; and 3.370±0.725 cm^3, respectively. The mean thickness of right, left, and total entorhinal cortex was 1.821±0.459 mm; 1.463±0.369 mm; and 3.285±0.791 mm, respectively. There is a possible difference between the early and late stages of AD in the same patient. Further studies with larger cohorts are needed to examine these correlations.

***Keywords**: Alzheimer's Disease, Head MRI, Hippocampus, Entorhinal Cortex*

Introduction

Alzheimer's disease is a progressive brain degenerative disease characterized by a gradual decline in memory or a disturbance in one of the highest intellectual functions[(1)]. Alzheimer's disease (AD) was the sixth leading cause of death in United States by Centers for Disease Control Prevention (CDC), accounting for 83,494 deaths in 2010[(2)].

Currently, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are the standard imaging evaluations in dementia. The most common MRI sequences are as follows: T1-Weighted Imaging (T1-WI), T2-Weighted Imaging (T2-WI), Fluid Attenuated Inversion Recovery (FLAIR), Diffusion Weighted Imaging (DWI), Gradient Echo (GRE) and acquisitions 3-Dimensional (3D) volume. Contrast imaging, Diffusion Tensor Imaging (DTI), Arterial Spin Labeling (ASL), and functional MRI might be useful but are not routinely performed[(3)].

Entorhinal cortex is a cortex that is partially covered by the rhinal (olfactory) sulcus. This cortex is the main part of medial temporal lobe, which plays an important role in memory system and the main connection between hippocampal formation and neocortex[(4)].

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Hippocampus is a cortical structure and is a part of medial temporal lobe where it is located inferiorly to lateral ventricle. This structure is involved in memory and neuroendocrine regulation. The hippocampus is a primitive cortex that plays a central role in memory processes with a relatively simple structure[4].

Information regarding hippocampus and entorhinal cortex sizes plays an important role in Alzheimer's disease. This study aims to determine hippocampal volume and entorhinal cortex thickness in Alzheimer's disease obtained from a group of patients who underwent head MRI.

Materials and Methods

Study Design

This study was an observational study with a retrospective approach that was conducted from July to December 2020 at a nursing home and a health care facility in Surabaya, Indonesia.

Study Subject

The study subjects were patients who were diagnosed with AD and met the inclusion and exclusion criteria. The inclusion criteria were all patients who were diagnosed by a neurologist with AD using MMSE, Hachinsky, and NIA-AA criteria and had available head MRI examination results. The exclusion criteria included individuals with a history of head trauma within the last 6 months and was found features of infarct and/or hemorrhagic stroke and/or tumor on their head MRI.

Data Collection

Demographic data and individual examination results were collected. In addition, data from individual head MRI examinations results were also collected.

The MRI machine used was General Electric (GE) Optima 360 1.5 T with GE Medical System software number 5394794-32. The MRI data used were taken from coronal slices of 3D-FSPGR MRI sequences. Entorhinal cortex thickness and hippocampal volume were measured with the following MRI settings: 3-Dimentional (3D) coronal slice, Fast Spoiled Gradient Echo (FSPGR), Time Echo (TE): 6, Time Repetition (TR): 13.2, Field of View (FOV): 24, slice thickness: 1.6, matrix: 320x192, bandwidth: 1563, and Inversion Time: 400.

Hippocampal volume and entorhinal cortex thickness measurements were performed manually using GE's Picture Archiving and Communication System (PACS) software with a single tracer. Hippocampal volume was measured in cubic centimeters (cm^3), while entorhinal cortex thickness was measured in millimeters (mm).

The assessment was conducted by two neuroradiology consultants, where each assessor did not know the patient's identity and data (double-blinded).

Data Analysis

The obtained data and hippocampal volume and entorhinal thickness measurement results were analyzed using SPSS version 21.0 software. The data analysis used descriptive statistics.

Results

Subject Characteristics

A total of 14 patients were diagnosed by a neurologist with AD using MMSE, Hachinsky, and NIA-AA criteria. Most AD patients were women with nine patients (64.3%).

The youngest patient with AD who underwent MRI examination was 61 years and the oldest was 85 years. The mean age of AD patients who underwent MRI examination was 75.14±8.085 years. Alzheimer's disease patients were then divided into two age groups, which were under and over 65 years. The results showed that Alzheimer's disease patients were mostly found in the age group of over 65 years with a total of 12 patients (85.7%).

Alzheimer's disease patients were also divided into two groups based on their latest education background, which were non-undergraduate and undergraduate groups. The results showed that most patients with Alzheimer's disease were in non-undergraduate group with 10 patients (71.4%). Data on subject characteristics of are presented in Table 1.

Table 1. Subject Demographic Characteristics

Characteristics	AD patients (N=14)
Mean age (years)	75.14 (8.085)
Gender (Male/Female)	5/9
Latest Education Background (Non-undergraduate/Undergraduate)	10/4
Duration of symptoms (years)	1.893 (1.318)
MMSE score	19.07 (4.16)

Hippocampal Volume and Entorhinal Cortex Thickness in AD Patients

Hippocampal volume and entorhinal cortex thickness measurements using head MRI were performed by two assessors. Kappa test was then performed on the first and second measurement results both on hippocampal volume and entorhinal cortex thickness. The kappa test values on hippocampal volume and entorhinal cortex thickness measurements were 0.714 and 0.851 respectively, with a significance value of 0.001 and 0.001. Results of the two assessors were then averaged, both for the hippocampal volume (right hippocampus, left hippocampus, total hippocampus) and entorhinal cortex thickness (right entorhinal cortex, left entorhinal cortex, and total entorhinal cortex).

Hippocampal volume and entorhinal cortex thickness measurements in AD patients were presented in the form of a box plot diagram to determine the existence of outliers. From the box plot diagrams on right, left, and total hippocampal volumes, no outlier was found (Figure 1a). Box plot diagrams on right, left, and total entorhinal thicknesses showed no outlier either (Figure 1b).

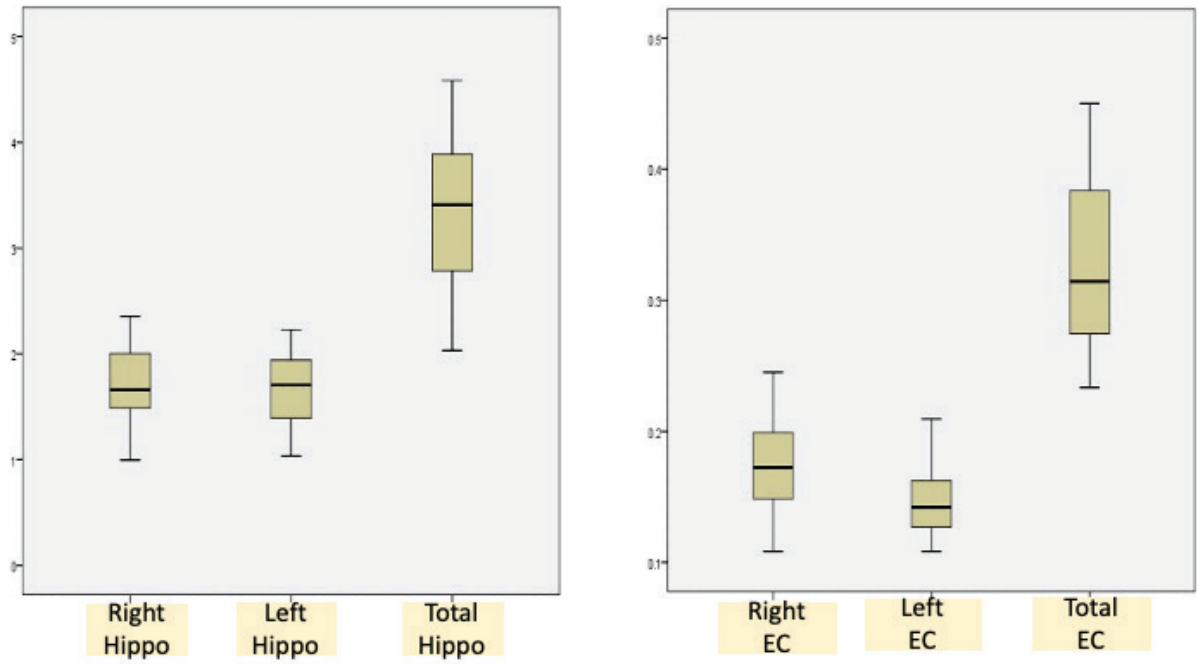

Figure 1. a. Box plot diagrams on right, left, and total hippocampal volume, b. Box plot diagrams on right, left, and total entorhinal thickness.

From head MRI measurement in AD patients, we found that the mean volume of right, left, and total hippocampal was 1700±0.395 cm^3; 1.670±0.349 cm^3; and 3.370±0.725 cm^3, respectively. The mean thickness of right, left, and total entorhinal cortex was 1.821±0.459 mm; 1.463±0.369 mm; and 3.285±0.791 mm, respectively. This data is presented in Table 2.

Table 2. Mean Entorhinal Cortex Thickness and Hippocampal Volume

Mean Size	Alzheimer's Disease Patients (N=14)
Right Hippocampal Volume (cm3)	1.700 (.395)
Left Hippocampal Volume (cm3)	1.670 (.349)
Total Hippocampal Volume (cm3)	3.370 (.725)
Right Entorhinal Cortex Thickness (mm)	1.821 (0.459)
Left Entorhinal Cortex Thickness (mm)	1.463 (0.369)
Total Entorhinal Cortex Thickness (mm)	3.285 (0.791)

Discussion

The youngest AD patient who underwent head MRI examination was 61 years old and the oldest was 85 years old. In this study, subjects suffering from Alzheimer's disease were divided into two age groups, which were <65 years and >65 years. The age group <65 years was included in the EOAD group (early onset AD) and the age group >65 years was included in the late onset AD or LOAD group[5]. Most patients with Alzheimer's disease were at above 65 years with a total of 12 patients. The age distribution in this study was the same as a study conducted by Van Der Vlies et al.[6], in 2009 where people with Alzheimer's disease above 65 years old had a greater proportion than people with Alzheimer's disease below 65 years old.

From a total of 14 patients with Azheimer's disease who underwent head MRI examinations, it was found that the incidence rate was higher for women than men. In this study, there were 9 female patients and 5 male patients. The gender distribution in this study was similar to a study from Viña and Lloret[7] in 2010 regarding the proportion of gender in people with Alzheimer's disease. The main risk factors for the development of AD are age and gender. The incidence of Alzheimer's disease was higher in women than men, and this could not simply be attributed to a higher life expectancy in women than in men. The explanation regarding the pathological process of higher incidence of Alzheimer's disease in women must be clearly explained. Viña and Lloret[7] explained that mitochondria in young women are protected from amyloid-β toxicity, less Reactive Oxygen Species (ROS) production by mitochondria, and less apoptogenic signal release. These mitochondrial protections were caused by the presence of estrogen hormone which protects cells from amyloid-β toxicity. Furthermore, estrogen level plummets in older women, reducing mitochondrial protection.

From 14 patients with Alzheimer's disease in this study, most patients (10 patients) had non-undergraduate education. With this data, it could be concluded that most of the study subjects had a lower level of education in this study. The result in this study was similar to a study by Sharp and Gatz[8] in 2011. This study[8] is a systematic review that analyzed a total of 88 studies, where 27 studies analyzed the correlation between education background and AD, 37 studies analyzed the correlation between education and total dementia, and 24 studies analyzed the correlation between the two (AD and total dementia). In this study, 51 studies (58%) reported a significant effect of low education on dementia risk, whereas 37 studies (42%) reported no significant correlation between low education and dementia outcome.

From the head MRI examination in Alzheimer's disease patients, hippocampal volume of entorhinal cortex thickness measurement was conducted using FSPGR sequence on coronal slices using manual tracer technique. From the head MRI measurement, it was found that the mean hippocampal volume in the right, left, and total hippocampus were 1.700±0.395 cm3; 1.670±0.349 cm3; and 3.370±0.725 cm3, respectively. The mean entorhinal cortex thickness in the right, left, and total entorhinal cortex were 1.821±0.459 mm; 1.463±0.369 mm; and 3.285±0.791 mm, respectively.

The mean hippocampal volume in this study has a minimal difference in a study from Dhikav et al.[9], where the results of the hippocampal volume were 1.64±0.55 cm3 in the right hippocampus and 1.59±0.55 cm3 in the left hippocampus. In another study from Vijayakumar and Vijayakumar[10] and Leandrou et al.[11], the hippocampal volume had a fairly wide margin, especially in a study from Leandrou et al.[11] because the study population did not represent the Asian race. Another factor that might have an effect is the severity of Alzheimer's disease patients in the study population and the size of the study population. The entorhinal cortex thickness in this study has a minimal difference in a study from

Holbrook et al.[12], where the mean entorhinal cortex thickness was 1.97±0.19 mm. In another study from Velayudhan et al.[13], the mean entorhinal cortex thickness had a fairly significant difference with of the entorhinal cortex thickness in this study, which 2.6±0.53 mm.

This study has several limitations. The number of subjects in this study was not large due to the high cost of MRI examinations and this examination is not covered by the patient's health insurance. Patients with severe Alzheimer's condition or restlessness could not have an MRI examination without the aid of anesthesia. It is possible that patients with severe conditions have lower hippocampal volume and entorhinal cortex thickness.

Conclusion

From the hippocampal volume measurements, it was found that the right, left, and total hippocampal volumes were 1.700±0.395 cm3; 1.670±0.349 cm3; and 3.370±0.725 cm3, respectively. Meanwhile, from the entorhinal cortex thickness measurements it was found that the right, left, and total entorhinal cortex thickness were 1.821±0.459 mm; 1.463±0.369 mm; and 3.285±0.791 mm, respectively.

There is a possible difference between the early and late stages of AD in the same patient, therefore the decrease in hippocampal volume and entorhinal cortex thickness could not be evaluated. Furthermore, continuous measurement of hippocampal volume and entorhinal cortex thickness might help predict AD progression and initiate early treatment. Further studies with larger cohorts are needed to examine these correlations.

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Ethical clearance

The protocol of this study was approved Institutional Ethics Committee, Faculty of Medicine, Airlangga University, Surabaya.

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