INTRODUCTION

Dementia refers to a clinical syndrome. Dementia is typically defined as an acquired condition marked by multiple cognitive impairments severe enough to impair daily functioning. In general, but not always, it is progressive. While memory impairment is an expected deficit, it is frequently associated with other domains such as language, praxis, visual-perceptive, and, most significantly, executive functions. Daily living activities become increasingly difficult due to progressive loss of function caused by these cognitive problems. A variety of pathophysiological processes can bring it about. The most prevalent type is Alzheimer’s disease, followed by vascular dementia.

Aging is the most prevalent cause of dementia. As the population ages and life expectancy increases, dementia is emerging as the century’s most serious public health problem. In Indonesia alone, it is estimated that there were approximately 1.2 million people living with dementia in 2016, a figure that will rise to two million by 2030 and four million by 2050. In 2016, dementia was estimated to cost USD 818 billion annually, a figure that is expected to rise to USD 1 trillion in 2018 and USD 2 trillion in 2030.

Magnetic resonance (MR) is a non-invasive examination. It could be used as a method in evaluating the structural and functional characteristics of the brain without the need for ionizing radiation. This means that longitudinal studies can be performed without considering the significant health risks of ionizing radiation.

Numerous studies have examined hippocampal atrophy and its relationship to aging and dementia, as well as the relationship between brain metabolic rates and aging and dementia. The purpose of this study was to calculate the amount of hippocampal volume loss associated with dementia as well as to examine the possible role of proton magnetic resonance spectroscopy (H-MRS) in common type of dementia.

ABSTRACT

Introduction: Dementia defined as an acquired condition marked by multiple cognitive impairments. The most prevalent type is Alzheimer’s disease, followed by vascular dementia. Studies have examined hippocampal atrophy and its relationship to aging and dementia. This study aimed to calculate the amount of hippocampal volume loss associated with dementia, also to examine the possible role of proton magnetic resonance spectroscopy (H-MRS) in common type of dementia.

Methods: This study compared hippocampal volume measures and metabolites level in posterior cingulate cortex (PCC) between Alzheimer’s disease patients, vascular dementia patients, and controls using volumetric-based MR and ‘H-MR spectroscopy. Metabolite levels were calculated from the peak integral value of the metabolite N-Acetyl Aspartate (NAA) (2 ppm), Myo-inositol (MI) (3.5 ppm), Cholin (Cho) (3.2 ppm), and Creatin (Cr) (3 ppm), then a comparison was made to the levels of brain metabolites in the form of: NAA / Cr, Cho / Cr, and MI / Cr.

Results: Between Alzheimer’s disease and control, a significant difference was observed in the total volume of the hippocampus of 20.45 % (p = 0.004). The comparison of brain metabolite levels in PCC patients with Alzheimer’s disease, vascular dementia, and control subjects revealed no statistically significant differences in the levels of Cholin, Creatine, NAA, Myo-inositol, Cho / Cr, NAA / Cr, and MI / Cr for any of the metabolites.

Conclusion: There was a significant difference in the mean total size of the hippocampus between patients with Alzheimer’s disease and controls, but not in the PCC metabolites measured by MR spectroscopy.

Keywords: Alzheimer’s disease, vascular dementia, hippocampal volume, posterior cingulate cortex (PCC), ‘H-Magnetic Resonance Spectroscopy (‘H-MRS).


Received: 2021-05-28
Accepted: 2021-07-20
Published: 2021-08-31

ORIGIANAL ARTICLE

P-ISSN.2089-1180, E-ISSN: 2302-2914

Hippocampal atrophy and levels of posterior cingulate cortex (PCC) metabolites in Alzheimer’s disease, vascular dementia and normal cognitive

Widiana Ferriastuti, Harianto Notopuro, Anggraini Dwi Sensusiti, Paulus Sugiarito

1Neuro Radiologist Consultant, Department of Radiology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia;
2Biochemistry Consultant, Department of Biochemistry, Faculty of Medicine, Airlangga University, Surabaya, Indonesia;
3Neuro Radiologist Consultant, Department of Radiology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia;
4Neurology Consultant, Department of Neurology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia;

*Corresponding author: Anggraini Dwi Sensusiti; Neuro Radiologist Consultant, Department of Radiology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia; anggraini-d-s@fk.unair.ac.id

Open access: www.balimedicaljournal.org
MATERIALS AND METHODS

Study Setting and the Data
This was a retrospective study conducted between July and December 2020 in a nursing home and a health facility in Surabaya. Patients with Alzheimer's dementia, vascular dementia and consent to received head MRI without contrast and MR spectroscopy included in this study. Dementia patients with previous history of depression, primary or metastase brain tumor and history of head tumor were excluded. This study involved 41 participants, 15 had Alzheimer's disease, 12 had vascular dementia and 14 had normal cognitive abilities. Neurology examined the participant who had a history of memory decline. All participants underwent a cognitive function assessment using the Mini-Mental State Examination (MMSE). A MMSE score of greater than 24 was considered normal. The control group consisted with healthy age-matched volunteers without the condition of neurological, psychiatric, or systemic disease.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was used to evaluate all study participants. Alzheimer's disease was diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke's and Alzheimer's Disease and Related Disorders Association's protocols (NINCDS–ADRDA).

Patients with vascular dementia diagnosed by implemented the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the International Association for Neuroscience Research Disorders and Stroke and the International (NINCDS–ADRDA).

The duration of symptoms along with comorbid conditions of the subjects included in this study was taken. Participants with a history of intracranial lesions, brain trauma, or acute stroke within the last six months were excluded from the study.

Instrument and MRI Protocol
The MRI and 1H-MRS were performed using the standard head coil on a clinical GE 1.5 T Optima 360 MRI. MRI protocol for hippocampus using 3-Dimensional (3D) Fast Spoiled Gradient Echo (FSPGR), coronal slices, Time Echo (TE): 6, Time Repetition (TR): 13.2, Field of View (FOV): 24, slice thickness: 1.6, matrix: 320 x 192, bandwidth: 1563, Inversion Time: 400. The volume of the hippocampus is determined by inserting a manual tracer into a coronal section of the hippocampus.1

1H-MRS was performed for quantification analysis of metabolite concentrations in the brain. 1H-MRS (Point Resolved Spectroscopy pulse sequence with TR / TE : 1000 / 144; flip angle=0°) was used to acquire spectra from a volume of interest (2x1x1.4 cm) located in the posterior cingulate cortex (PCC). Spectroscopic data acquisition uses 3D images of the sagittal, coronal and axial planes as a guide for localization of the voxels of interest.

Metabolite levels were calculated from the peak integral value of the metabolite N-Acetyl Aspartate (NAA) (2 ppm), Myo-inositol (MI) (3.5 ppm), Cholin (Cho) (3.2 ppm), and Creatin (Cr) (3 ppm), then a comparison was made to the levels of brain metabolites in the form of: NAA / Cr, Cho / Cr, and MI / Cr.

Two neuroradiologists analyzed raw data on hippocampal volume measurements simultaneously to ensure that they applied the same criteria independently. When the results were inconclusive between the two observers, they were confirmed by another experienced neuroradiologist. More experienced neuroradiologists record metabolite levels during MR spectroscopy. All neuroscientists were not aware of all clinical data on study subjects.

Data Analysis
Descriptive data were analyzed accordingly, with mean and standard deviation (SD) for normal distribution of data and median for data without normal distribution. For data with normal distribution, ANOVA and post hoc analysis was performed to distinguish between groups in terms of hippocampal volume and PCC spectroscopic metabolites. The Kruskal-Wallis and Mann Whitney tests were used to analyze data with an abnormal distribution. Prior to conducting the comparison test, the Shapiro Wilk test was used to determine the normality of the data distribution within each study group. The group classified as Alzheimer’s disease group, vascular dementia group and control group. A p value < 0.05 was used as the level of statistical significance.

RESULTS
The study population included a total of 41 subjects (15 with alzheimer's disease, 12 with vascular dementia and 14 as control). There was no significant difference in sex, age, or education between groups. The demographic characteristics of the subjects included in the study, along with duration of symptoms and the MMSE score included in Table 1.

Two assessors performed measurements on the right and left hippocampus with a kappa value of 0.778 and 0.852, respectively (p = 0.001). Right-left hippocampus mean values in Alzheimer's disease, vascular dementia and controls were 1.716 ± 0.386 cm³ and 1.671 ± 0.336 cm³ respectively; 2.036 ± 0.372 cm³ and 1.956 ± 0.415 cm³, and 2.19 ± 0.319 cm³ and 2.068 ± 0.286 cm³, respectively.

Significant volume reduction of +/-20.45 percent was observed when the Alzheimer's disease group compared to the control group (p = 0.004). As depicted in Table 2, when the Alzheimer's group was compared to the vascular dementia group and the vascular dementia group to the control group, no significant decrease in volume was observed (p = 0.071 and 0.59, respectively). Between vascular dementia and alzheimer's disease, the mean total volume of the hippocampus decreased by 15.15 %, whereas between vascular dementia and control, the mean total volume of the hippocampus decreased by 6.25 %.

The comparison of brain metabolite levels in PCC patients with Alzheimer’s disease, vascular dementia, and control subjects revealed no significant differences in the levels of Cholin, Creatine, NAA, MyoInositol, Cho / Cr, NAA / Cr, and mI / Cr for any of the metabolites (p = 0.144; 0.051; 0.846; 0.445; 0.618; 0.197; and 0.262, respectively). Complete information regarding the levels of PCC metabolites can be seen in Table 3.


**DISCUSSION**

This study compared hippocampal volume measures and metabolites level in PCC between patients with Alzheimer’s, patients with vascular dementia, and controls using volumetric-based MR and $^1$H-MR spectroscopy. The mean age for Alzheimer’s disease group was 76.27 years, vascular dementia group was 74.5 years, while the control group was 72.5 years.

Previous study by Schmidt et al. found that the average age of patients with probable Alzheimer’s disease was 68.2 years. For vascular dementia, the mean age was 69.9 years while 66.3 years for healthy controls. We discovered that 55.55 percent of cases were classified as Alzheimer’s disease and 44.45 percent as vascular dementia. Schmidt et al. found that 53.4 percent of patients had probable Alzheimer’s disease and 46.6 percent had vascular dementia.

The MMSE score was used to determine the severity of dementia in this study. The current conducted study found that the mean MMSE score for Alzheimer’s disease was 19.27. The mean MMSE score for vascular dementia was 21.08, while control cases was 29. According to Vijayakumar et al., the mean MMSE score for Alzheimer’s disease cases was 18.18. However, for vascular dementia it was 12.4 while mixed dementia cases was 13. The mean MMSE score for normal pressure hydrocephalus (NPH) was 22.50. Our study found that the mean total hippocampal volume of Alzheimer’s disease patients was $3.388 \pm 0.702 \text{ cm}^3$, that of patients with vascular dementia was $3.993 \pm 0.762 \text{ cm}^3$, and that of controls was $4.259 \pm 0.588 \text{ cm}^3$ (Table 2).

There is a significant difference in the total volume of the hippocampus of 20.45 % ($p = 0.004$) between Alzheimer’s disease and control. This is consistent with research conducted by Vijayakumar et al., in which a statistically significant difference ($p = 0.002$) was observed between the Alzheimer’s disease and control groups, as well as a 25% volume reduction in the Alzheimer’s disease group. In our study, there was no statistically significant difference in the total volume of the hippocampus between Alzheimer’s disease and vascular dementia or between vascular dementia and control ($p = 0.071$.

---

**Table 1. Demographic Characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer’s disease n = 15</th>
<th>Vascular dementia n = 12</th>
<th>Control n = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>76.27 ± 8.924</td>
<td>74.5 ± 6.948</td>
<td>72.5 ± 4.735</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>6/9</td>
<td>7/5</td>
<td>4/10</td>
</tr>
<tr>
<td>Duration of education (years), mean ± SD</td>
<td>8.67 ± 5.01</td>
<td>9.17 ± 4.366</td>
<td>12.29 ± 2.301</td>
</tr>
<tr>
<td>Symptoms duration (years)</td>
<td>1.967 ± 1.302</td>
<td>1.583 ± (1.4275</td>
<td>-</td>
</tr>
<tr>
<td>MMSE, mean ± SD</td>
<td>19.27 ± 4.079</td>
<td>21.08 ± 2.109</td>
<td>29 ± 0.961</td>
</tr>
</tbody>
</table>

**Table 2. Hippocampal volume in subjects.**

<table>
<thead>
<tr>
<th></th>
<th>Right Hippo</th>
<th>Left Hippo</th>
<th>Total Hippo</th>
<th>P value of VaD vs AD vs Control*</th>
<th>P value of VaD vs Control*</th>
<th>P value of AD vs Control*</th>
<th>P value of AD vs VaD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD, mean ± SD</td>
<td>1.716 ± 0.386</td>
<td>1.671 ± 0.336</td>
<td>3.388 ± 0.702</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VaD, mean ± SD</td>
<td>2.036 ± 0.372</td>
<td>1.956 ± 0.415</td>
<td>3.993 ± 0.762</td>
<td>0.005</td>
<td>0.59</td>
<td>0.004</td>
<td>0.071</td>
</tr>
<tr>
<td>Control, mean ± SD</td>
<td>2.19 ± 0.319</td>
<td>2.068 ± 0.286</td>
<td>4.259 ± 0.588</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Comparison based on the average hippocampal total volume

AD: Alzheimer’s disease, VaD: vascular dementia

**Table 3. PCC Metabolite levels in Subjects**

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>VaD</th>
<th>Control</th>
<th>P value of AD vs VaD vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho, mean ± SD</td>
<td>82110.60 ± 28856.63</td>
<td>87203.42 ± 50402.14</td>
<td>59601.14 ± 33637.15</td>
<td>0.144</td>
</tr>
<tr>
<td>Cr., mean ± SD</td>
<td>87617.93 ± 57828.73</td>
<td>86231.75 ± 44970.24</td>
<td>53299.71 ± 34282.09</td>
<td>0.051</td>
</tr>
<tr>
<td>NAA, mean ± SD</td>
<td>94916.00 ± 46610.42</td>
<td>99044.00 ± 61809.05</td>
<td>87275.14 ± 51125.94</td>
<td>0.846</td>
</tr>
<tr>
<td>MI, mean ± SD</td>
<td>55761.27 ± 25355.11</td>
<td>47174.58 ± 25123.93</td>
<td>45487.36 ± 17907.29</td>
<td>0.445</td>
</tr>
<tr>
<td>Cho/Cr, mean ± SD</td>
<td>1.19 ± 0.58</td>
<td>1.08 ± 0.45</td>
<td>1.32 ± 0.74</td>
<td>0.518</td>
</tr>
<tr>
<td>NAA/Cr, mean ± SD</td>
<td>1.31 ± 0.67</td>
<td>1.13 ± 0.44</td>
<td>1.84 ± 1.15</td>
<td>0.197</td>
</tr>
<tr>
<td>MI/Cr, mean ± SD</td>
<td>0.90 ± 0.66</td>
<td>0.68 ± 0.49</td>
<td>1.03 ± 0.493</td>
<td>0.262</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease, VaD: vascular dementia
MRS is frequently used to detect and study metabolite concentrations in the cerebral area. These include Myo-Inositol (mI), choline (Cho), N-acetyl aspartate (NAA), and creatine (Cr). These particular metabolites associated with a pathological process located at the brain. NAA is a neuron-specific marker, in which mitochondria is responsible for its synthesis. A regional reduction in NAA, as measured with MRS, is widely accepted as a sign of neuronal dysfunction caused by reduction in neuronal density, loss of neuronal cell, or partially reversible neuronal dysfunction. The signaling by Cho majorly mediated by free glycerophosphocholine and phosphocholine. When they attached to the membrane of the cell, each of the substance are immobile. However, in situation where the cell membrane is ruptured, they become mobile, eventually contributed to the Cho signal. Since the creatine levels are relatively stable, the Cr level is used as a reference point. mI, it has been proven as a marker for glial activation, an osmolyte. The substance also part of a component of the second messenger system.

The assessment of brain metabolite levels in PCC patients with Alzheimer’s disease, vascular dementia, and control subjects revealed no significant difference in the levels of Cholin, Creatine, NAA, mI, Cho/Cr, NAA/Cr, and mI/Cr (p = 0.144; 0.051; 0.846; 0.445; 0.618; 0.197; and 0.262). In a systematic review by Wang et al., there were 17 studies examining metabolite levels in the posterior cingular cortex. A total of 15 studies examine the NAA / Cr ratio. The total sample size was 1,544 participants, consisted of 970 healthy controls and 614 Alzheimer’s disease). The posterior cingulate cortex was found to have a significant decrease in the NAA / Cr ratio with a high degree of heterogeneity. Twelve studies examined Cho / Cr ratios in the posterior cingulate and found that the ratio was significantly increased with moderate heterogeneity. The mI / Cr ratio was investigated in fourteen studies, and a significant increase in the posterior cingulate was observed with moderate heterogeneity. Additionally, four studies examined the mI / NAA ratio and discovered that it increased significantly in the absence of heterogeneity.

However, based on the average value of metabolite levels, it was determined that Cholin, Creatin, NAA, and mI levels increased by 27.41 and 31.65 percent, 39.17 and 38.19 percent, 8.05 and 11.88 percent, and 18.42 and 3.58 percent, respectively, when Alzheimer’s disease was compared to control and Vascular dementia was compared to control. Meanwhile, the Cho / Cr, NAA / Cr, and mI / Cr ratios decreased by 9.85 percent and 18.18 percent, 28.8 percent and 38.59 percent, and 12.62 percent and 33.98 percent, respectively, in comparisons between Alzheimer’s disease and control and between vascular dementia and control.

In this study, there was a significant difference in the mean total size of the hippocampus between patients with Alzheimer’s disease and controls, but not in the PCC metabolites measured by MR spectroscopy.

Numerous limitations existed in this study. Patients were not examined during the course of their disease. There are likelihood of differences between early and late stages of dementia for the particular same patient. The hippocampal atrophy in the late stage of a dementia subtype could be indiscernible from hippocampal atrophy in the early stage of another dementia subtype. Participants with severe dementia were not subjected to an MRI examination in this study because patients with severe dementia required anesthesia assistance in order to undergo the examination. Hippocampal volume measurements cannot be performed on participants with severe dementia, affecting the study’s results.

CONCLUSION

There was a significant difference in the mean total size of the hippocampus between patients with Alzheimer’s disease and controls, but not in the PCC metabolites measured by MR spectroscopy. The best method for differentiating between study groups is still hippocampal volume measurement. The spectroscopic method for determining metabolite levels needs to be reexamined, particularly in PCC, despite previous studies demonstrating significance. In general, the use of spectroscopic methods to differentiate between dementias requires additional research.


