International Journal of Gerontology 17 (2023) 110–113
https://doi.org/10.6890/IJGE.202304_17(2).0006

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Original Article

Correlation of MI/NAA with MMSE in Alzheimer's Dementia

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ARTICLE INFO

Accepted 12 July 2022

Keywords:
Alzheimer dementia,
hippocampal,
myoinositol,
N-acetylaspartate

SUMMARY

Background: The delay and increase in the number of Alzheimer's dementia patients cause many impacts, both from increased morbidity and moral and material losses. Biomarkers such as brain imaging (magnetic resonance imaging (MRI) and positron emission tomography (PET) Scan) need to be done immediately in the diagnosis of suspected Alzheimer's dementia. This study aimed to analyze the relationship between the hippocampal myo-inositol (MI)/ N-acetylaspartate (NAA) ratio and the severity of Mini-Mental State Examination (MMSE) in Alzheimer's dementia patients.
Methods: MMSE and Hachinski scores were assessed by a neurologist, and the hippocampal mI/NAA ratio was calculated using MRI and MR spectroscopy.
Results: The right hippocampal MI/NAA was significant with the incidence of Alzheimer's (p value = 0.018).
Conclusion: There was a correlation between right MI/NAA and the severity of MMSE in Alzheimer's dementia patients.

1. Introduction

Alzheimer's dementia (AD) is an irreversible progressive brain disorder, namely a decrease in the brain's thinking ability. The majority of AD symptoms appear at the age of 60 years.[1] N-acetylaspartate (NAA), myo-inositol (MI), and Choline (Cho) are metabolites high enough in the brain to be measured by magnetic resonance spectroscopy (MRS) and are often analyzed in dementia.[2]

AD was classified using three types of biomarkers to determine the level of typical pathology of AD using the amyloid (A), tau (T) and neurodegenerative (N) classification. The A/T/N classification of each individual was assessed as positive (+) as abnormal and negative (-) as normal for each biomarkers. The reference values for pathological cerebrospinal fluid (CSF) biomarker were ≤ 192 pg/mL for Aβ42, ≥ 93 pg/mL for t-tau and ≥ 23 pg/mL for p-tau.[3]

MI is one of the brain metabolites measured *in vivo* through spectroscopic MR examination. MI acts as a neuroglial marker and maintains neuroglial volume in astrocytes. A similar study was conducted by Siger et al., (2009) that the increase in MI may occur due to the activation of microglia from the inflammatory process and the presence of amyloid deposition. This situation indicates that increased MI may occur more clearly and more sensitively as an indication of Alzheimer's pathology than NAA.[3]

NAA is another brain metabolite for interpreting the function of neuronal structures, located in neurons and concentrated in the cytosol. The process of accumulation of Aβ oligomers will result in neurotoxicity and neuromuscular damage, resulting in a decrease in NAA marked by neuronal loss and volumetric change.

Globally, the incidence of AD until 2020 has covered more than 50 million people. It is predicted that the increase of AD cases will continue to increase in 2030 to 82 million people and 152 million people in 2050.[1] In Indonesia, the incidence of AD in 2015 has experienced more than 1.2 million people with an estimated increase of 1.8 million people in 2030 and 3.9 million people in 2035.[4]

The diagnosis of AD can be made with several clinical efforts such as cognitive or neurological examination, brain imaging (magnetic resonance imaging (MRI) and positron emission tomography (PET) Scan) and CSF analysis to determine the severity of Mini-Mental State Examination (MMSE) in AD patients.[5]

Research on MI/NAA was conducted by Welikovitch et al., (2020) in experimental animals, it was found that an increase in mI/NAA results in astrocyte activity and proliferation in the hippocampus. In addition, the study also stated that there was a decrease in the value of NAA indicating a neuronal loss in AD.[6] The same situation occurs in the human brain, that in AD patients the NAA value is low, while the hippocampal mI value has 1 rarely been studied previously.[7]

With this background, the researchers were interested in analyzing the correlation of MI/NAA with the severity of MMSE in AD patients.

2. Material and methods

The research was conducted ethical clearance at Dr. Soetomo General Hospital from January to December 2020 with the code number 1879/KEPK/III/2020. The study was conducted with a cross-sectional design to assess the right-left hippocampal MI/NAA ratio in AD patients. The population in this study is the elderly over 60 years

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who are suspected of having dementia or dementia by heteroanamnesis. The research sample was all patients with AD with a diagnosis by a neurologist using the MMSE, Hanchinsky, National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association and MRI criteria from Panti Wredha Surabaya.

The inclusion criteria for the study were patients with suspected AD, male or female with an examination by a neurologist with MMSE criteria (score < 24), Hachincky (score < 4), aged 60 years and over, agreed to give informed consent and were willing to undergo MRI and MR spectroscopy. The sample will be excluded when it is stated that there is a history of brain injury in the last 6 months and a picture of a stroke infarct in the hippocampus area and/or strategic location or bleeding stroke and the tumor is found on the results of the MRI examination of the sample.

The sampling technique was carried out with consecutive techniques according to the inclusion criteria until the required research sample size was met. The number of samples calculated by the formula Snedecor & Cochran (1967) and Lemeshow (1997) obtained the total final sample of 50 people, namely 28 samples of AD patients and 22 samples of non-AD patients.

The data collected from the hippocampal MI/NAA ratio was carried out by MRI and MRS. The tools used in the MRI are general electric (GE) 1,5 T type Optima 360 and software GE Medical System No. 5394794-32. MRS was carried out using GE 1,5 T type Optima 360 and software GE Medical System No. 5394794-32 with multivoxel sequence. The settings made to measure metabolic variables are: TR/TE (1000/144; flip angle: 0°) is used to obtain the spectrum of the desired volume ($2 \times 1 \times 1.4$ cm) located in the right-left hippocampus. Metabolite levels were calculated from the peak integral values of the metabolites of MI 3.5 ppm and NAA 2 ppm, then a comparison of the levels of brain metabolites in MI/NAA was performed.

The statistical analysis of the normality of the research data was carried out by the Kolmogorov test. In testing the correlation between variables used the Mann-Whitney Test and Spearman's Rho it can be seen the path analysis of the influence between variables on the incidence of AD.

3. Results

3.1. Respondents characteristics

The majority of AD occurred in the elderly 65 years old (89.3%) with the oldest being 92 years old and the youngest 61 years old. Most AD occurred in women, namely 60.7%. The majority of 82.1% of AD suffers have an educational background below the tertiary level (Table 1).

Table 1
Respondent characteristics.

Characteristics	AD		Non-AD		Total	
	n	%	n	%	n	%
Age (years old)						
≥ 65	25	89.3	20	90.9	45	90
60–64	3	10.7	2	9.1	5	10
Gender						
Female	17	60.7	14	63.6	31	62
Male	11	39.3	8	36.4	19	38
Education						
≥ Bachelor	5	17.9	5	22.7	10	20
< Bachelor	23	82.1	17	77.3	40	80
Total	28	100	22	100	50	100

3.2. MMSE frequency distribution

Most of the MMSE scores of AD were in the mild category. The highest MMSE value of 23 occurred in 5 samples, while the lowest MMSE value of 9 occurred in 1 sample. All non-AD had normal MMSE values with the highest score of 30 in 6 samples and the lowest score of 26 in 1 sample (Table 2).

3.3. Right-left hippocamal MI/NAA ratio in Alzheimer's dementia patients

This study resulted in a statistical value that there was a significant relationship between right-left hippocampal MI/NAA in Alzheimer's and non-AD patients. The left hippocampus of Alzheimer's patients appears lower than that of non-AD patients. The patient's right hippocampus showed the highest values of 1.8 and 1.46 on the left hippocampus, with the lowest values being 0.20 on the right hippocampus and 0.23 on the left hippocampus. Non-Alzheimer's patients had the highest left hippocampal MI/NAA value of 2.72 and the lowest of 0.08. On the right hippocampus the highest score was 1.03 with the lowest value being 0.19 (Table 3).

3.4. Total hippocampal volume in Alzheimer's dementia

Patients with dementia Alzheimer's had the highest total hippocampal volume value of 5.55 cm^3 with the lowest value of 2.03 cm^3. In non-Alzheimer's patients, the highest total hippocampal volume value was 5.56 cm^3 and the lowest value was 3.16 cm^3 (Table 4).

4. Discussions

4.1. Respondents characteristics

As many as 89.3% of AD aged > 60 years while the same thing also happened in the normal comparison group of 90.9%. Age is a major risk factor for AD and continues to increase with age. The incidence of AD in the elderly tends to occur due to a decrease in physi-

Table 2
MMSE frequency distribution.

MMSE	AD		Non-AD		Total	
	n	%	n	%	n	%
Normal (≥ 25)	0	0	22	100	22	44
Mild (18–24)	22	78.6	0	0	22	44
Moderate (10–17)	5	17.8	0	0	5	10
Severe (≤ 9)	1	3.6	0	0	1	2
Total	28	100	22	100	50	100

Table 3
Right-left hippocampal MI/NAA ratio in Alzheimer's dementia.

Variable	MI/NAA			
	Right hippocampus		Left hippocampus	
	Mean ± SD	p value	Mean ± SD	p value
AD	0.89 ± 0.44	0.018	0.69 ± 0.36	0.922
Non-AD	0.61 ± 0.25		0.82 ± 0.69	

Table 4
Total hippocampal volume in Alzheime's dementia.

Variable	Total hippocampal volume	
	Mean ± SD	p value
AD	0.69 ± 0.36	0.922
Non-AD	0.82 ± 0.69	

cal activity and cognitive function so that the synapse process in the hippocampus is disrupted.[8]

Women in their 60 years tend to have a higher acquired hypogonadotropic hypogonadism so they are more likely to suffer from AD (Alzheimer's Association 2016) gender differences can be a risk factor for AD because it undergoes endocrine changes during perimenopause.[9]

Educational characteristics of AD are almost entirely educated below bachelor's degree by 82.1%, while for the non-AD group, most if they are educated below bachelor's degree by 77.3%. The Shanghai Epidemiological Survey of Dementia and Alzheimer's Disease and the Shanghai Aging Study research found a relationship between education level and AD. An increasing trend in the prevalence and incidence of dementia was also found in the Chinese elderly, especially those with low education.[10]

4.2. Right-left hippocamal MI/NAA ratio in Alzheimer's dementia patients

The significance of the MI/NAA ratio was found only on the right side of the hippocampus. In several other studies, only the comparison of the total MI/NAA ratio in the posterior cingulate cortex (PCC) was carried out. In the study of Wang et al., (2009) revealed a significant increase in the hippocampal MI/NAA ratio when compared to PCC and cognitive decline.[11]

The case and control groups had significant differences in the ratio NA/Cr, MI/Cr and MI/NAA in the PCC area, and the ratio of MI/Cr and MI/NAA in the hippocampal formation. MI and NAA are the two most influential metabolites in AD, with ratio calculations found an increase in MI concentration by gliosis and a decrease in NAA due to neuronal damage.[12]

An increase in the MI/NAA ratio is an early sign of Alzheimer's. A similar study was conducted by Wang et al., (2015) by calculating the MI/NAA ratio in the combined right and left hippocampus versus the PCC MI/NAA ratio in Alzheimer's, MCI and control groups. The results showed that there was a combined significance of the right and left hippocampus and an increase in MI in the hippocampus of Alzheimer's patients along with an increase in glial content.

Research by Barnes et al., (2009) and Shi et al., (2009) stated that patients with Alzheimer's have an asymmetrical hippocampal size, namely the right side is larger than the left side. As the severity of Alzheimer's increases, the impact changes on the left side compared to the right side.[13,14]

Research by Wang Z, et al. (2009) revealed that the increase in the hippocampal MI/NAA ratio was more significant that the posterior cingulate, and this was in accordance with the pathological process of AD. The MI/NAA ratio in the hippocampus and in the posterior cingulate area differentiated between AD, MCI and control groups. There is a significant correlation between the MI/NAA ratio and cognitive decline.[11]

In this study, we found a correlation between right-sided hippocampal volume measurements that were greater on the right than on the left side and an increased MI/NAA ratio in AD patients. The asymmetry that occurs where the left side is smaller than the right side is in accordance with the statement of Shi, et al. (2009). Changes in brain metabolites in the form of an increase in MI are due to the activation of microglia from the inflammatory process and amyloid deposition, while a decrease in NAA occurs from neurotoxic conditions on the right where there is the accumulation of Aβ oligomers accompanied by neuronal damage. This increase in MI is a clearer and more sensitive indication of AD pathology (Siger 2009).

Various things that affect this condition in terms of structural changes, namely volume, surface area, interhemispheric length and in terms of functional differences where the left hemisphere is the dominant hemisphere for verbal cognitive function and the right hemisphere is the dominant hemisphere for spatial and mood functions.[15]

4.3. Total hippocampal volume in Alzheimer's dementia

Hippocampal volume calculations were performed using the T1W image method from brain MRI. Hippocampal volume values were calculated with a standard protocol. In the statistical calculation of this study, it was found that the total hippocampal volume was significant with AD (Pearson correlation coefficient = -0.54; $p < 0.05$).

A similar study conducted by Vijayakumar (2013) on the comparison of cases of AD in the case and control groups found significance ($p < 0.001$) for right versus left hippocampal volume and hippocampal ratio.[16]

Research by Dubois, Picard, & Sarazin (2009) and Raji, Lopez, Kuller, & Becker (2009) states that the hippocampus specifically exhibits specific areas of atrophic patterns that begin in the transentorhinal cortex and then progress through the entire structure. Structural MR studies demonstrated development of hippocampal atrophy in the demented stage of MCI is a very accurate predictive marker of progression to AD.[17,18]

The rate of hippocampal atrophy in Alzheimer's patients can be a sign for the diagnosis and evaluation of AD. Every year there continues to be a difference in hippocampal atrophy, namely 4.66% in Alzheimer's patients and 1.4% in non-Alzheimer's. Several factors that influence the difference in the rate of hippocampal atrophy include the severity of Alzheimer's, co-existing vascular disease, previous drug administration, Apolipoprotein E gene status and measurement methods and slice thickness or segmental protocols.[13] Hippocampal volume reduction has been shown to have a strong correlation with progression to AD and changes significantly over time in individuals with late mild cognitive impairment. It can be concluded that there is a correspondence between the theory and research findings, and there is a correlation between differences in the speed of hippocampal atrophy with the incidence of AD.

A similar study conducted by Yamaguchi et al. (1997) showed a correlation of decreased glucose metabolism on PET examination with hippocampal atrophy on MRI. The study sample of mild AD experienced more severe metabolite asymmetry on the right side than on the left side and vice versa. Yamaguchi's study is consistent with this study that samples of AD with mild severity produced a more significant metabolite MI/NAA ratio in the right hippocampus than on the left.

5. Conclusion

The results of this study found that the right hippocampal MI/NAA ratio was higher than the left hippocampus in Alzheimer's patients. Hippocampal volume is smaller in Alzheimer's patients than in non-Alzheimer's. A correlation was found between right hippocampal MI/NAA and total hippocampal volume in AD patients. The suggestion that can be given in this study is the measurement of hippocampal volume would be better using intracranial volume.

Conflict of interest

There are no conflicts of interest which are declared by the authors regarding this paper.

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