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Beta Amyloid and Malondialdehyde Serum Levels' Analysis in Atrial Fibrillation Patients with Cognitive Impairment

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Abstract:

Background: Atrial fibrillation (AF) is the most commonly encountered cardiac dysrhythmia, and AF patients are five times more likely to have a risk of stroke. Although the effects of stroke on patients are quite severe, lately it has been recognized that AF is associated with the incidence of cognitive impairment and dementia.

Objective: This study aims to analyze and determine the differences in two isoforms of amyloid beta (Aββ40 and 42) and malondialdehyde (MDA) serum levels in AF patients who experience and who do not experience cognitive impairment.

Methods: An observational study with case-control design was carried out on 63 people with atrial fibrillation, consisting of 38 people with cognitive impairment and 25 people without cognitive impairment. Examination of MDA and the Aβ40 and Aβ42 levels was carried out by ELISA. The difference level of each variable in the two groups was tested by the Mann–Whitney and χ^2 tests, at $P \leq 0.05$ significance level.

Results: Lower mean levels of Aβ42 and higher mean levels of MDA were found in the group with cognitive impairment rather than in the group without cognitive impairment. Lower mean levels of Aβ40 were found in the group with cognitive impairment rather than in the group without cognitive impairment but this difference was not statistically significant.

Conclusion: Significantly lower levels of Aβ42 and higher levels of MDA were found in the AF patients with cognitive impairment rather than in the AF patients without cognitive impairment.

Key Words:

Atrial fibrillation, beta amyloid, cognitive impairment, malondialdehyde

Key Message:

Cognitive impairment in patients with atrial fibrillation can occur even without being preceded by a stroke. It is suspected that it occurs through the amyloid beta cascade disorders and stress oxidative due to cerebral hypoxia occurs in patients with atrial fibrillation.

Cognitive impairment is one of the most common neurological problems found in atrial fibrillation (AF) patients, also often associated with dementia, even though the patients have not experienced a stroke. The underlying mechanisms are still unclear, but there are several proposed mechanisms including embolic stroke, silent brain infarction, microbleeding, and cerebral hypoperfusion.[1]

Atrial fibrillation often provides minimal symptoms but still can cause cerebral hypoperfusion. Silent brain infarction is often found in atrial fibrillation patients and it is believed to be one of the mechanisms that underlie the cognitive impairment.[2] Elderly patients with silent brain infarctions have an increased risk of dementia and cognitive impairment over those who do not have these lesions.[3] Gaita *et al.* found that the prevalence of silent brain infarction was about three times higher in patients with AF compared to those patients with sinus rhythm.[4]

There is plenty of evidence that suggests that cerebral ischemia plays an important role in the development of Alzheimer's disease; for example, an animal trial suggests that brain ischemia can

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cause an accumulation of amyloid precursor protein (APP) and beta amyloid (Aβ).[5,6] Some hypotheses regarding the relationship between AF and dementia have been proposed, including a suggestion that cerebral hypoperfusion in AF causes damage to neuron cells and thus contributes to the etiology of dementia.[7] Some have suggested that AF directly affects AD neuropathology, such as senile plaques and neurofibrillary tangle, but there is an uncertain evidence for this explanation. Dublin *et al.* found higher levels of senile plaques and neurofibrillary tangles in patients with permanent AF rather than in non-AF patients.[8]

The mechanism of cognitive impairment in various hypoxic conditions, almost certainly involves a disruption of the beta amyloid cascade. It has been shown that recurrent hypoxic conditions can stimulate an increased breakdown of amyloid precursor protein (APP) through the activation of beta enzyme and gamma secretase, which will increase the production of Aβ.[9-11]

In conditions of reduced blood flow (oligomia), the pro-oxidant and antioxidant balance is disrupted and causes an increased production of free radicals. Although the process of cognitive impairment and dementia is related to several etiologies and pathophysiological mechanisms, oxidative stress is recognized as a major part of the pathophysiological process.[12] One form of oxidative reaction results in brain tissue that is rich in unsaturated fatty acids (polyunsaturated fatty acids/PUFAs) and can be screened for with malondialdehyde. Bradley-Whitman and Lovell found that the markers of lipid peroxidation not only can be seen in the advanced phase of cognitive impairment but also can be seen in earlier phases.[13]

Thus, it is still unclear whether cognitive impairment or dementia in AF patients happens because of or is accompanied by neuropathological changes, such as in Alzheimer's disease. According this study was undertaken to assess the serum levels of β-amyloid isoforms Aβ40 and Aβ42, and malondialdehyde (MDA) in nonvalvular AF patients who experienced cognitive impairment and compare them in AF patients without cognitive impairment.

Methods

Sample collection

An observational study with case-control design was conducted in 63 participants with atrial fibrillation, in cardiology outpatient clinic of Dr. M. Djamil and Ibnu Sina Islamic Hospital Padang, from March 1 to September 25, 2017. This present study passed ethical clearance by the research ethics committee of the Faculty of Medicine of Andalas University. Atrial fibrillation diagnoses were made via an electrocardiogram examination conducted by a cardiologist. All patients with atrial fibrillation who never experienced stroke and other degenerative diseases such as Alzheimer's and Parkinson's were included. Sample collection was done by consecutive sampling, in which all the subject that meet the inclusion criteria were included.

Cognitive function examination was assessed by the Montreal Cognitive Assessment–Indonesian Version (MoCA-Ina); the Indonesian version of the MoCa has been separately validated. There are some questionnaires used for cognitive impairment screening, but we choose MoCA-Ina because it is more applicable, measures some cognitive domains and it can use on transcultural population. Cognitive function was determined normal if MoCA-Ina score ≥26 and cognitive impairment if MoCA-Ina score <26. We added one point of MoCA-Ina score if participant undergoes less than 12 years education. Cognitive impairment diagnosis was based on MoCA-Ina test (clinical manifestation) without radiological examination. The examination was done by a neurologist. Subjects of this study were divided into two groups based on the MoCa-Ina test, i.e. cognitive impairment and without cognitive impairment groups. Examination of Aβ40, Aβ42 and malondialdehyde (MDA) serum was done by ELISA.

Statistical analysis

The basic characteristics' data differences in both groups were analyzed by Chi-square (χ^2) and the Mann–Whitney tests. The difference level of each variable (Aβ and MDA) in the two groups was tested by *t*-test, if the data were normally distributed, and the Mann–Whitney test if the data were not, but the normality test could not be used in this study. Differences were statistically significant if the *P* value <0.05.

Results

Based on MoCA-Ina result, on 63 participants, we found 38 participants with abnormal MoCa-Ina score (MCI) and 25 participants with normal score. Table 1 shows that the basic characteristics (age, sex, and education) between the case group (AF patients with cognitive impairment) and the control group (AF patients with normal cognitive function) were not significantly different ($P > 0.05$). The median value of MOCA-Ina in the nonvalvular AF group with cognitive impairment was 24 with the lowest 13 and the highest 25, and for the group without cognitive impairment, the median score was 27 with the lowest 26 and the highest 29. In this study, three variables were examined, specifically, the levels of Aβ40, Aβ42 and MDA serum as determined by ELISA.

The differences of beta-amyloid and malondialdehyde levels in the nonvalvular AF group with and without cognitive impairment are shown in Table 2. We found Aβ40 levels were lower in the AF group with cognitive impairment than in the AF group without cognitive impairment, but this difference was not statistically significant ($P = 0.273$). The Aβ 42 levels were lower in the AF group with cognitive impairment than in the AF group without cognitive impairment, and here the difference was statistically significant ($P = 0.012$). The MDA levels were higher in the AF group with cognitive impairment rather than in the AF group without cognitive impairment and the difference was statistically significant ($P = 0.033$).

Discussion

This is currently a growing concern that AF has an association with an increased risk of dementia and Alzheimer's disease; thus, it is believed that intervention for AF can reduce the incidence of dementia and Alzheimer's disease. Therefore, it is important to know its pathophysiology. Cognitive impairment in patients with AF can occur without having a history of stroke at first.[14,15] The risk to suffer a cognitive impairment is relatively similar between AF patients who have experienced a stroke and those who have not.[15] This study did not include the people with previous stroke history,

Table 1: Basic characteristic of the two groups

Basic characteristics	Study Subjects		*P*
	Cognitive impairment (*n*=38)	Normal Cognitive Function (*n*=25)	
Age	55.50 (35-67)	45 (38-67)	0.275**
Sex			
Male	9	11	0.954*
Female	16	27	
Education (Year)	12 (6-18)	16 (6-16)	0.058**
MoCA-Ina (Cognitive Function)	24 (13-25)	27 (26-29)	<0.001**

*χ^2 test, **Mann-Whitney test

Table 2: The differences of beta-amyloid and malondialdehyde levels in the nonvalvular atrial fibrillation group with and without cognitive impairment

Variable	Research Subjects		*P*
	Cognitive Impairment (*n*=38)	Normal Cognitive Function (*n*=25)	
Aβ40 Serum Level	138.69 pg/ml (23.96-860.26)	169.78 pg/ml (12.75-549.33)	0.273*
Aβ42 Serum Level	113.73 pg/ml (23.6-667.86)	148.04 pg/ml (42.21-708.57)	0.012*
MDA Serum Level	210.44 ng/ml (22.24-338.95)	185.54 ng/ml (2.26-334.01)	0.033*

*Mann-Whitney test

dementia, and other neurodegenerative disease. There were no significant differences based on basic characteristics (age, sex, and education) between the AF patients with cognitive impairment and without cognitive impairment.

We found that Aβ42 levels were lower in the AF group with cognitive impairment rather than in the AF group without cognitive impairment, and this difference was statistically significant ($P = 0.012$). The Aβ40 levels were also lower in the group with cognitive impairment but did not differ statistically.

Various studies have shown that the underlying cause of cognitive impairment in patients with Alzheimer's dementia is a disruption of synapses by Aβ. Physiologically, a low concentration of Aβ in the brain is needed to regulate and maintain the plasticity of the synapse and to improve cognitive function; however, higher concentrations of Aβ accumulation will cause damage to this regulatory function with the consequences of dysfunction and damage of synapse, as seen in dementia patients.[16-18]

Elevation of Aβ levels in the brain not only can cause LTP damage but also cause damage to the protrusions, which are found on the surface of the dendrites and function as impulse recipients from the nerve cells. The damaged protrusions are found around amyloid plaques in the brains of dementia patients, as well as in animal models.[19,20]

The main pathological sign of Alzheimer's disease is the discovery of extracellular amyloid plaques in the brain followed by intracellular neurofibrillary tangle formation. In normal conditions, the formation of beta amyloid from Amyloid Precursor Protein (APP) with the help of beta and gamma secretase occurs but its clearance also occurs in a balanced way. If the balance of beta amyloid formation and clearance is disrupted, beta amyloid accumulation can occur. Thus, the failure of beta amyloid clearance is believed to be one of the pathogenic causes of Alzheimer's disease. The accumulation of amyloid beta due to a failure of the clearance process can occur for years or even one or two decades before clinical symptoms appear.[21]

Chronic cerebral hypoperfusion is thought to potentially explain the relationship between AF and cognitive impairment. Hypoxia that occurs during hypoperfusion has been shown to increase the expression of beta and gamma secretase, so that the Aβ production increases.[22] This is shown by the elevation of plasma Aβ levels after experiencing cardiac arrest.[23] Elevation of Aβ production causes various effects on brain blood vessels including increased arterial pressure due to vascular vasoconstriction, decreased cerebral blood flow, reduced endothelium vasodilation ability, and impairment of increasing CBF capability following increased neuronal activity.[24,25] At the end of this process, the atherosclerosis of blood vessels in the brain will occur.

Aβ clearance from the brain into systemic circulation occurs in several ways, such as degradation by the neprilysin enzyme and insulin-degrading enzymes, reabsorption by cerebrospinal fluid, clearance through the vascular mechanism with a help of lipoprotein receptor-related protein 1, and perivascular drainage.[26] In a recent study, it was found that almost 50% of Aβ clearance occurs through blood vessel absorption into the CSS and perivascular drainage.[27] Along with various processes that occur in the cerebral blood vessels due to an increase of Aβ formation, such as vasoconstriction, its clearance process can also experience interference due to changes in blood vessel walls, with the result that the amount of Aβ in the brain will be excessive, while the overall systemic levels will decrease.

The low serum levels of Aβ42 and Aβ40 in the AF group with cognitive impairment compared to the AF group without cognitive impairment are estimated to occur because of the disruption of the Aβ clearance from the brain to the systemic circulation, which causes an accumulation of Aβ in the brain and cognitive impairment.

In this study, we found Aβ40 levels were lower in the AF group with cognitive impairment rather than in the AF group without cognitive impairment, but the difference was not statistically significant. This may be related to several factors that were not designed to be measured in this study, such as the duration of AF and age factors.

Besides hypoxia, Aβ42 is a powerful generator of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can stimulate lipid peroxidation both *in vitro* and *in vivo*.[28] Malondialdehyde (MDA) is one of the toxic aldehydes produced due to lipid peroxidation, which will cause damage to mitochondrial enzymes. Oxidative stress and Aβ are related to each other because Aβ stimulates the formation of oxidative stress both *in vitro* and *in vivo* and oxidative stress alone increases the production of Aβ.[29]

In this study, we found an increase of MDA serum levels in the AF group with cognitive impairment compared to the AF group without cognitive impairment, and the difference was statistically significant. The higher level of MDA indicates an increase in oxidative stress pathway activity. Oxidative stress can affect cognitive function through different biological mechanisms.[30] Liu *et al.* also found a higher level of MDA in poststroke cognitive impairment cases compared to the nonpoststroke cognitive impairment group.[30]

Conclusion

We found lower Aβ42 serum levels and higher MDA levels in the AF group with cognitive impairment rather than in the AF group without cognitive impairment.

Research limitations

This study only illustrates that in the AF group with cognitive impairment, Aβ42 levels were lower and MDA levels were higher compared to the AF group without cognitive impairment. The study design did not permit assessment of other various factors that could influence the occurrence of cognitive disorders, such as age, duration of illness, and the effect of drugs that have been used. This study also did not examine Aβ40 and Aβ42 concentration on normal population with similar age range. Therefore, it is necessary to do further research to examine other factors that could influence the incidence of cognitive disorders in AF.

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Conflicts of interest

There are no conflicts of interest.

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