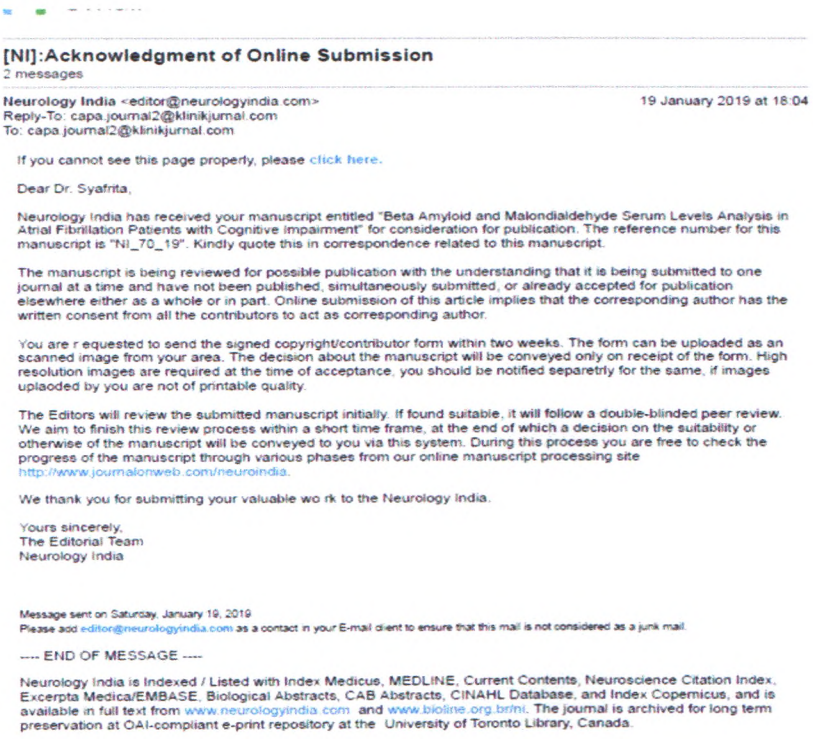
Kronologis Proses Pemasukan *(Submission)* Artikel hingga Terbit (*Published*) Pada *Publisher* Neurology India

Judul Artikel	:	Beta Amyloid and Malondialdehyde Serum Levels Analysis in Atrial Fibrillation Patients with Cognitive Impairment
Jurnal	:	Neurology India
Halaman	:	5 halaman
SJR	:	Quartil Q3 dengan SJR 0,339
Submitted	:	19 Januari 2019
Revised	:	15 Nopember 2019
Revised Version	:	10 Desember 2019
Accepted	:	28 Januari 2020
Technical and language edit	:	29 Februari 2020
Revised technical and Language Edit	:	1 Maret 2020
Accepted	:	15 Mei 2021
Galley Proof Check	:	20 Agustus 2021
Revised Galley Proof	:	22 Agustus 2022
Publish	:	3 May 2022

KRONOLOGIS SEBAGAI BERIKUT

1. Manuscripe di submit di Jurnal Neurology India pada tanggal 19 Januari 2022 (gambar 1).



[NI]:Acknowledgment of Online Submission
2 messages

Neurology India <editor@neurologyindia.com> 19 January 2019 at 18:04
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Gambar 1. paper di submit

Respon pertama dari editor, diterima pada 25 Maret 2019, dan manuscripe menjalani review oleh editor dan Peer dan pada tanggal 15 Nopember 2019 baru ada report review (gambar 2)

[NI]:Article for revision:NI_70_19
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Neurology India <editor@neurologyindia.com> 15 November 2019 at 13:35
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With reference to your manuscript entitled 'Beta Amyloid and Malondialdehyde Serum Levels Analysis in Atrial Fibrillation Patients with Cognitive Impairment', please review the comments of the referees from our s ite http://www.journalonweb.com/neuroindia. The manuscript would be reconsidered after requisite modifications as per the comments and instructions provided by the journal.

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With warm personal regards,

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Neurology India
Remarks:

[REVIEWER]:

This study evaluated serum Beta Amyloid and malondialdehyde levels in Atrial Fibrillation (AF) patients with and without cognitive impairment in 63 patients. They hypothesize that cognitive impairment in AF patients happen because of or are accompanied by neuropathological changes such as Alzheimer's disease and study results showed lower Aβ42 serum levels and higher MDA levels in the AF group with cognitive impairment compared to AF group without cognitive impairment. The strength of the study is that it is an observational study with a case control design and was done systematically to investigate the underexplored hypothesis.

Gambar 2 Report of Review

2. Revisi di kirim ke editor pada tanggal 10 Desember dan respon dari editor diterima pada tanggal 28 Januari dan menyatakan bahwa manuscripe dengan status Provisional Accepted (Accepted sementara) gambar 3

[NI]:Article provisionally accepted.:NI_70_19
1 message

Neurology India <editor@neurologyindia.com> 28 January 2020 at 12:47
To: capa.journal2@klinikjurnal.com

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Gambar 3, Status manuscripe : Provisional Accepted

3. Selanjutnya manuscripe menjalani technical dan language edit dan baru dinyatakan Accepted pada 15 May 2021 (Gambar 4)

[NI]:Decision on your article:NI_70_19
1 message

NI <editor@neurologyindia.com> 15 May 2021 at 21:20
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Dear Dr. Syafrita,

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Neurology India

Gambar 4. Status Manuscripe : Accepted

4. Galley Proof dikirim tanggal 20 Agustus 2021 (gambar 5) dan perbaikannya di kirim ke editor jurnal pada tanggal 22 Agustu 2021(Gambar 6)

[NI]:Article for final proof:NI_70_19

From Neurology India on 2021-08-20 10:53

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Gambar 5 : Galley Proof

[NI]:We have received your inputs:NI_70_19

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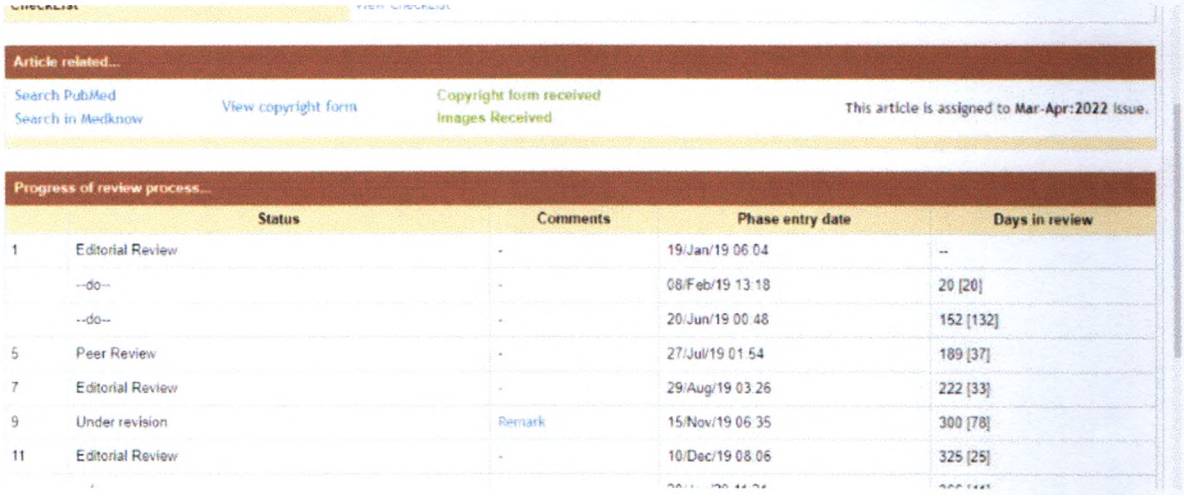
Gambar 6 : Revised Galley Proof

5. Perkiraan Publish

Dinyatakan bahwa artikel akan terbit pada edisi Maret-April 2022, seperti gambar 7.



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5	Peer Review	-	27/Jul/19 01:54	189 [37]
7	Editorial Review	-	29/Aug/19 03:26	222 [33]
9	Under revision	Remark	15/Nov/19 06:35	300 [78]
11	Editorial Review	-	10/Dec/19 08:06	325 [25]

Lampiran A

Artikel Awal

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

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Abstract
Introduction: 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 is quite severe, lately it has been recognized that AF is associated with the incidence of cognitive impairment and dementia, regardless of whether there is a previous history of stroke or not. It was also reported that the incidence of dementia was twice as high in AF patients and there was a significant relationship between cognitive impairment and AF. This study aims to analyze and determine the differences in two isoforms of amyloid beta (Aβ40 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 impairments and 25 people without cognitive impairment. Examination of MDA and the Aβ40 and Aβ42 levels were carried out by ELISA. The difference level of each variable in the two groups was tested by the Mann–Whitney test, and the relationship between each variable with the presence of cognitive impairment was tested by the chi-square test, each at a $p \leq 0.05$ 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 and this difference was statistically significant. 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.

Keywords: Atrial fibrillation, beta amyloid, cognitive impairment, malondialdehyde.

Introduction

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 a 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 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 the prevalence of silent brain infarction was about three times higher in patients with AF compared to those patient 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 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 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. Bredley 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 happen because of or are accompanied by neuropathological changes, such as in Alzheimer's disease. Accordingly, 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 people 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. Subjects of this study was 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.

Statitical Analysis

The basic characteristics data differences in both groups were analyzed by chi-square and the Mann–Whitney test. 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

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**

*Chi-Square

**Uji Mann–Whitney

The table above shows that the basic characteristics (age, sex and education) between the case group (AF patients with cognitive impairments) 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 score of 13 and the highest 25; for the group without cognitive impairment, the median score was 27 with the lowest score of 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 Atrial Fibrillation Patients with Cognitive Impairment and Without Cognitive Impairment

The differences of beta-amyloid and malondialdehyde levels in the non-valvular AF group with and without cognitive impairment as can be seen in Table 2.

Table 2. The Differences of Beta-Amyloid and Malondialdehyde levels in the Non-Valvular 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

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] 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 a 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 patents, 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, failure of beta amyloid clearance it 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, 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 is 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]. Z. Liu also found a higher level of MDA in post-stroke cognitive impairment cases compared to the non-post-stroke cognitive impairment group.[30]

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. Therefore, it is necessary to do further research to examine other factors that could influence the incidence of cognitive disorders in AF.

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.

Conflict of Interest

There is no conflict interest in this research.

Acknowledgements

The author thank to Andalas University for facilitating this research.

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Lampiran B

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

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Abstract
Introduction: Atrial fibrillation (AF) is the most commonly encountered cardiac dysrhythmias and AF patients are five times more likely to have a risk of stroke. Although the effect of stroke on patients is quite severe, lately it has been known that AF is associated with the incidence of cognitive impairment and dementia, regardless of whether there was a previous history of stroke or not. It was also reported that the incidence of dementia was twice as high in AF patients and there was a significant relationship between cognitive impairment and AF. This study aims to analysis and determine the differences of amyloid beta (Aβ) 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 impairments and 25 people without cognitive impairment. Examination of Aβ levels (40 and 42) and MDA was carried out by the Elisa method. The difference level of each variable in the two groups was tested by Mann Whitney test and the relationship between each variable with the presence of cognitive impairment, was tested by chi-square test. It is statistically significant if the p value is ≤ 0.05. **Results:** A 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 and this difference was statistically significant. A 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: A 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.
Keywords: Atrial fibriation, beta amyloid, cognitive impairment, malondialdehyde.

Introduction

Cognitive impairment is one of the most common neurological problems that was found in atrial fibrillation (AF) patients, not only in the form of cognitive impairment, but also often associated with the incidence of dementia, even though the patient do not experienced a stroke. Underlying mechanisms is still unclear, but there are several mechanisms that though to be happened including embolic stroke, silent brain infarction, microbleeding and cerebral hypoperfusion[1].

Atrial fibrillation often provides minimal symptoms, but still can cause a cerebral hypoperfusion. Silent Brain Infarction is often to be found in atrial fibrillation patients and it is believed to be one of the mechanisms that underlying the cognitive impairment[2]. Eldery with a silent brain infarction have an increased risk of dementia and cognitive impairement that is steeper than those who do not have these lesions[3]. Gaita et al. found the prevalence of silent brain infarction was about 3 times higher in those patient with AF compared to those patient with sinus rhythm.[4]

There are a plenty of evidence which suggest that cerebral ischemia plays an important role in the development of Alzheimer's disease and an animal trial suggests that brain ischemia can cause an accumulation of amyloid precusor protein (APP) and beta amyloid (Aβ) [5,6]. Some hypotheses regarding the relationship between AF and dementia have been proposed, including a hypotheses which suggest that cerebral hypoperfusion in AF causes a damage to neuron cells and thus contributes to the etiology of dementia[7] and another hypothesis also said that AF directly affects AD neuropathology, such as senile plaques and neurofibrillary tangle, but there is an uncertain evidence for this explanation. Dublin found a higher levels of senile plaques and neurofibrillary tangle in patients with permanent AF rather than in non AF patients.[8]

The mechanism of cognitive impairment in various hypoxic conditions, almost involves a disruption of the beta amyloid cascade. It has been shown that recurrent hypoxic conditions can stimulate an increase breakdown of amyloid precursor protein (APP) through the activation of beta enzyme and gama secretase which will increases the production of Aβ[9,10,11].

In the conditions of reduced blood flow (oligomia) pro-oxidants and antioxidants balance will be disrupted and will cause an increased production of free radicals. Although the process of cognitive impairement and dementia is related to several etiologies and pathophysiological mechanisms, oxidative stress is recognized as a major part of its pathophysiological process[12]. One form of oxidative reactions results in brain tissue which is rich of unsaturated fatty acids

(polyunsaturated fatty acids / PUFAs) is malondialdehyde. Bredley found that the markers of lipid peroxidation, not only can be found in the advanced phase of cognitive impairment, but also can be found in the earlier phase[13].

Based on the background that was stated above, it is still unclear whether cognitive impairment or dementia in AF patients is happen through out neuropathological changes, such as in the Alzheimer's disease, accordingly, the researchers wanted to know the serum levels of β-amyloid (Aβ) 40, β amyloid (Aβ) 42, and malondialdehyde (MDA) in nonvalvular AF patients who experienced cognitive impairment compared to those without cognitive impairment.

Methods

Sample Collection

An observational study with case-control design was conducted in 63 people with atrial fibrilation, in cardiology outpatient clinic of DR.M.Djamil and Ibnu Sina Islamic Hospital Padang, from the periode of 1st march 2017 until 25th september 2017. This present study has passed ethical clearance which was issued by research ethics committee of Faculy of Medicine of Andalas University. Atrial fibrillation diagnosis was made by an electrocardiograms examination that was conducted by a cardiologist. All patient with atrial fibrillation who never experienced stroke and other degenerative disease such as Alzheimer's and Parkinson were included. Sample collection was done by concecutive sampling, which all the subject that meet the inclusion criteria were included. Cognitive function examination was assessed by Montreal Cognitive Assesment of Indonesian version (MoCA-Ina), which is one kind of neuropsychological test that has been developed into Indonesian version and has been validated. Subjects of this study was divided into two group based on the MoCa-Ina test, a cognitive impairment and without cognitive impairment subjects. Examination of Aβ40, Aβ42 and malondialdehyde (MDA) serum was done by Elisa methode.

Statitical Analysis

The basic characteristics data differences in both groups were analyze by chi square and Mann-Whitney test. The difference level of each variable (Aβ and MDA) in the two groups was tested by t test if the data was normally distributed and Mann Whitney test if the data was not normally distributed, but normality test could not be used in this study. Data was statistically significant if p value <0.05.

Results

Table 1. Basic characteristic of the two groups

Basic Characteristic	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**

*Chi-Square

**Uji Mann-Whitney

The table above shows that the basic characteristics (age, sex and education) between the case group (AF patients with cognitive impairments) and the control group (AF patients with normal cognitive function) were no significantly difference(p> 0.05) or it means that both groups are equal. The median value of MOCA-Ina in the nonvalvular AF group with cognitive impairment was 24 with the lowest score of 13 and the highest in 25. While for the group without cognitive impairment, the median score was 27 with the lowest score of 26 and the highest 29.

In this study 3 variables were examined, specifically, the levels of Aβ40, Aβ42 and MDA serum with the Elisa methode.

The Differences of Beta-Amyloid and Malondialdehyde Levels in the Atrial Fibrillation Patients with Cognitive Impairment and Without Cognitive Impairment

The differences of beta-amyloid and malondialdehyde levels in the non-valvular AF group with and without cognitive impairment as can be seen in the table below:

Table 2. The Differences of Beta-Amyloid and Malondialdehyde levels in the Non Valvular Atrial Fibrillation Group with and without Cognitive Impairment

Variable	Research Subjects		
	Cognitive Impairment (n = 38)	Normal Cognitive Function (n = 25)	p
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

We found Aβ40 levels were lower in the AF group with cognitive impairment rather than in the AF group without cognitive impairment and this difference was not statistically significant ($p > 0.05$). The Aβ 42 levels were lower in the AF group with cognitive impairment rather than in the AF group without cognitive impairment and the difference was statistically significant ($p < 0.05$). 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 ($p < 0.05$).

Discussion

This is currently a growing issue that AF has association with an increased risk of dementia and Alzheimer's disease. It is believed that intervention of 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 stroke and who have not experienced stroke.[15]

There were no significant differences based on basic characteristic (age, sex, and education) between the AF patients with cognitive impairment and without cognitive impairment ($p > 0.05$), which is meant that the basic characteristic between the case group and control group was statistically equivalent.

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 low 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 the synapse 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 the higher concentrations of Aβ accumulation will

cause a 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 will causes a LTP damage, but also will causes a protrusions damage which is found on the surface of the dendrites, where these protrusions function as an impulses recipients from the nerve cells. The damaged protrusion dendrites is found around the amyloid plaque in the brains of dementia people, as well as in animals[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 beta and gamma secretase help and its clearance occurs in a balance way. If the balance of beta amyloid formation and clearance is disrupted, beta amyloid accumulation will occurs. A Failure of beta amyloid clearance it is believed to be one of the pathogenesis of Alzheimer's disease. The accumulation of amyloid beta due to a failure of the clearance process has occurred for years or even 1-2 decades before clinical symptoms appear[21].

Chronic cerebral hypoperfusion is estimated could explain the relationship between AF and cognitive impairment. Hypoxia that occurs during hypoperfusion has been shown could increase the expression of beta and gamma secretase, so that the Aβ production will increase[22]. This is proven 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 which following an increased neuronal activity[24,25]. At the end of this process, atherosclerosis of blood vessels in the brain will occur.

The Aβ clearance from the brain to 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]. From a recent study, it was found that almost 50% of Aβ clearance occurs through blood vessels absorption into CSS and perivascular drainage[27]. Along with various processes that occur in the cerebral blood vessels due to increased of Aβ formation, such as vasoconstriction, its clearance process also experiencing interference due to

changes in blood vessel walls, with the result that the Aβ in the brain will overload, while in the 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, is estimated to occur because of the disruption of the Aβ clearance from the brain to the systemic circulation, which will causes an accumulation of Aβ in the brain, and then will underlie the 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 do not analyzed 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 secies (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 the mitochondrial enzyme. 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 increased of oxidative stress pathway activity. Oxidative stress can affect cognitive function through different biological mechanisms[30]. Liu Z also found ahigherr levels of MDA in post stroke cognitive impairment cases compared to the non-post-stroke cognitive impairment group[30].

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. Researchers cannot assess other various factors that influence the occurrence of cognitive disorders, such as age, duration of illness and the effect of drugs that have been used. Therefore, it is necessary to do further research which can examine more factors that influence the incidence of cognitive disorders in AF.

Conclusion

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

Conflict of Interest

There is no conflict interest in this research.

Acknowledgements

The author thank to Andalas University for facilitating this research.

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