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

Judul Artikel	: Relationship between Plasma Level of Beta-amyloid, Alpha-synuclein and Tau Protein with Cognitive Impairment in Parkinson disease
Jurnal	: Open Acces Macedonian Journal of Medical Sciences
Halaman	: 5 halaman
SJR	: Quartil Q3 sampai dengan 2020
Submitted	: 12 November 2021
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KRONOLOGIS SEBAGAI BERIKUT

1. Email pemberitahuan tertanggal 12 November 2021(**Gambar 1**) dari editor Open Access Macedonian Journal of Medical Sciences, bahwa artikel sudah dikirim (**submitted**). *Original paper* diberikan pada **Lampiran A**

[OAMJMS] Submission Acknowledgement
1 message

Prof. Dr Mirko Spiroski via SFS - Journals (Scientific Foundation SPIROSKI - Journals), Skopje, Republic of Macedonia <noreply@publicknowledgeproject.org> 12 November 2021 at 15:48
Reply-To: "Prof. Dr Mirko Spiroski" <mspiroski@yahoo.com>
To: Yuliarni Syafrita <yuliarni.syafrita@klinikjurnal.com>

Yuliarni Syafrita:

Thank you for submitting the manuscript, "Relationship between plasma level of beta-amyloid, alpha-synuclein and tau protein with cognitive impairment in Parkinson disease" to Open Access Macedonian Journal of Medical Sciences. With the online journal management system that we are using, you will be able to track its progress through the editorial process by logging in to the journal web site:

Submission URL: https://oamjms.eu/index.php/mjms/authorDashboard/submission/7940
Username: dr_yuliarni

If you have any questions, please contact me. Thank you for considering this journal as a venue for your work.

Prof. Dr Mirko Spiroski

Gambar 1. Email Author's original Submission

2. Email pemberitahuan tertanggal dari 6 Januari 2022 dari Editor Open Access Macedonian Journal of Medical Sciences,(**Gambar 2**) tentang hasil **review dari Reviewer.**

[OAMJMS] Editor Decision 1 message **Mirko Zhivko Spiroski via SFS - Journals (Scientific Foundation SPIROSKI - Journals), Skopje,Republic of Macedonia** <noreply@publicknowledgeproject.org>6 January 2022at 15:31Reply-To: Mirko Zhivko Spiroski <mspiroski@yahoo.com>

To: Yuliarni Syafrita <yuliarni.syafrita@klinikjurnal.com>, Attiya Istarini <tya.handrian@gmail.com>, Syarif Indra<indraneuro@yahoo.com>, Restu Susanti <restususanti@yahoo.com>

Yuliarni Syafrita, Attiya Istarini, Meldayeni Busra, Syarif Indra, Restu Susanti (Author):We have reached a decision regarding your submission to Open Access Macedonian Journal of Medical Sciences,"Relationship between plasma level of beta-amyloid, alpha-synuclein and tau protein with cognitive impairment inParkinson disease", Manuscript ID = OJS7940.Our decision is: Revise your manuscript until January 30, 2022 and submit on the OAMJMS website.Sincarely,Prof. Dr Mirko Spiroski,Editor-in-Chief, OAMJMS

Scientific Foundation SPIROSKI,Rajko Zhinzifov No 48,1000 Skopje,Republic of Macedonia

----------Reviewer B:

The paper needs wide editing, since several grammatical errors are present and some expressions need an Englishnative language touch.

Hoen and Yahr scales is written erroneously all over, it is Hoehn (!).

Do not say stadium; stage is the right word and authors have already used it up and down.

Please clarify if there are wide, multicentric and validated studies regarding the laboratory methodology used toevaluate the proteins imputed with cognitive impairment in PD.

Recommendation: Revisions Required----------

Gambar 2. Komentar reviewer

3. Hasil Revisi dikirim ke editor Open Access Macedonian Journal of Medical Sciences pada tanggal 13 Januari 2022 dan di balas pada tanggal 5 maret yang menyatakan bahwa status manuscripe adalah **Accepted** (gambar 3) **Hasil revisi pada Lampiran B**

[OAMJMS] Editor Decision
1 message

Mirko Zhivko Spiroski via SFS - Journals (Scientific Foundation SPIROSKI - Journals), Skopje, Republic of Macedonia <noreply@publicknowledgeproject.org> 5 March 2022 at 16:26
Reply-To: Mirko Zhivko Spiroski <mspiroski@yahoo.com>
To: Yuliarni Syafrita <yuliarni.syafrita@klinikjurnal.com>, Attiya Istarini <tya.handrian@gmail.com>, Syarif Indra <indraneuro@yahoo.com>, Restu Susanti <restususanti@yahoo.com>

Yuliarni Syafrita, Attiya Istarini, Meldayeni Busra, Syarif Indra, Restu Susanti (Author):

We have reached a decision regarding your submission to Open Access Macedonian Journal of Medical Sciences, "Relationship between plasma level of beta-amyloid, alpha-synuclein and tau protein with cognitive impairment in Parkinson disease", Manuscript ID = OJS7940.

Our decision is to: Accept your revised manuscript for publication in OAMJMS.

Scientific Foundation SPIROSKI,
Rajko Zhinzifov No 48,
1000 Skopje,
Republic of Macedonia

Gambar 3, Manuscripe revision : Accepted

4. Editor jurnal memberi tahu tanggal 21 maret 2022, bahwa editing submission telah komplit dan siap dikirim ke tim production (gambar 4)

[OAMJMS] Editor Decision
1 message

Teodora Fildishevska via SFS - Journals (Scientific Foundation SPIROSKI - Journals), Skopje, Republic of Macedonia <noreply@publicknowledgeproject.org> 21 March 2022 at 17:45
Reply-To: Teodora Fildishevska <tfildishevska@id-press.eu>
To: Yuliarni Syafrita <yuliarni.syafrita@klinikjurnal.com>, Attiya Istarini <tya.handrian@gmail.com>, Syarif Indra <indraneuro@yahoo.com>, Restu Susanti <restususanti@yahoo.com>

Yuliarni Syafrita, Attiya Istarini, Meldayeni Busra, Syarif Indra, Restu Susanti (Author):

The editing of your submission, "Relationship between plasma level of beta-amyloid, alpha-synuclein and tau protein with cognitive impairment in Parkinson disease," Manuscript ID = OJS7940 is complete. We are now sending it to production.

Submission URL: https://oamjms.eu/index.php/mjms/authorDashboard/submission/7940

Gambar 4 bahwa artikel siap dikirim ke tim produksi

5. Editor memberi tahu pada tanggal 30 Maret 2022, bahwa artikel sudah **Publish (Lampiran C)**

[OAMJMS] Your Article was Published
1 message

MSc, Eng Ivo Spiroski via SFS - Journals (Scientific Foundation SPIROSKI - Journals), Skopje, Republic of Macedonia <noreply@publicknowledgeproject.org> 30 March 2022 at 16:14
Reply-To: "MSc, Eng Ivo Spiroski" <ispiroski@id-press.eu>
To: Yuliarni Syafrita <yuliarni.syafrita@klinikjurnal.com>

Dear Yuliarni Syafrita,

Please note that your paper "Relationship between Plasma Level of Beta-amyloid, Alpha-synuclein, and Tau Protein with Cognitive Impairment in Parkinson Disease", was published in Open Access Maced J Med Sci (OAMJMS).

DOI: https://doi.org/10.3889/oamjms.2022.7940

Username: Yuliarni Syafrita

Thank you for your fine contribution. On behalf of the Editors of the Open Access Macedonian Journal of Medical Sciences, we look forward to your continued contributions to the Journal.

Cordially,
Prof. Dr Mirko Spiroski,
Editor-in-Chief

Gambar 5 bahwa artikel sudah Publish

Lampiran A

PAPER DENGAN VERSI PERTAMA KALI DIKIRIM (ORIGINAL VERSION)

Judul Artikel and	: Relationship between Plasma Level of Beta-amyloid, Alpha-synuclein Tau Protein with Cognitive Impairment in Parkinson disease
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Relationship between Plasma Level of Beta-amyloid, Alpha-synuclein and Tau Protein with Cognitive Impairment in Parkinson disease

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Abstract

Background: Most people with Parkinson's disease will develop dementia along with their illness development. There are overlapping pathological images in the brains of patients with Parkinson's and Alzheimer's disease, related to the findings of pathological proteins of beta amyloid, alpha synuclein and tau protein. This study to asses cognitive impairment and relation with plasma level of beta-amyloid, alpha synuclein and tau protein in Parkinson disease.

Methods: A case-control design study was conducted on 62 people with Parkinson's disease and 20 healthy adults as control. Patients with Parkinson's disease were divided into groups with and without cognitive disorders based on the Montreal Cognitive Assessment Indonesian version (MoCA-Ina). The levels of beta-amyloid, alpha-synuclein, and tau protein were examined using the enzyme-linked immunoassay technique. Differences in levels between healthy adults, the Parkinson's disease group with and without cognitive disorders, were tested using Student's t-test if the data were normally distributed and the Mann–Whitney U test if the data were not normally distributed with the ´significance of 0.05 (p-value < 0.05).

Results: The differences in the plasma levels of beta-amyloid, alpha-synuclein, and tau protein were found between the control group and the Parkinson' s disease group ($p < 0.05$). It was also found differences in beta amyloid levels in Parkinson's disease group with and without cognitive impairment ($p < 0.05$) but none in other parameters ($p > 0.05$).

Conclusion: Low plasma levels of beta-amyloid 42 (Aβ42) are associated with cognitive disorders in patients with Parkinson's disease.

Keywords: Parkinson's disease, cognitive disorders, beta-amyloid, alpha-synuclein, tau protein

Introduction

Along with the increasing life expectancy, degenerative diseases also show a significant rise in numbers. Parkinson' s disease is one of the most neurodegenerative disease, **whom** shows a similar pattern of increasing incidence. Parkinson' s disease is known for its prominent motoric and non-motoric symptoms. Cognitive impairment is one of non motoric symptoms that greatly interfere with development of Parkinson's disease. People with Parkinson's disease more likely three to six times to develop dementia than those of the same age without the disease.[1,2,3] Other reports suggest that the lenght of illness Parkinson's disease will increased risk of dementia. At the beginnig of Parkinson disease, cognitive impairment was found in 25% of cases, and **while** this condition continues so that it is reported that 80% will become dementia[4,5,6]

The presence of alpha synuclein in the brains of patients with Parkinson's disease is a major pathological finding, and Its existence can be in the form of lewys body or lewys neurite.

However, from the immunohistochemical examination of this synuclein, it was also found in a fairly large area of The presence of alpha synuclein in the brains of patients with Parkinson's disease is a major pathological finding, and Its existence can be in the form of lewys body or lewys neurite. Likewise amyloid plaques and neurofibrillary tangles are found 30-40% in the brains of Parkinson's patients in postmortem studies. This fact further convinces an overlapping pathological process between Parkinson' s and Alzheimer' s diseases and certainly influences the appearance of symptoms in patients.[5,10] Several studies suspect a strong relation of pathological features of Alzheimer' s disease with the appearance of cognitive disorders in Parkinson' s disease.[11,12,13] Research has found that the pathological combination of alpha-synuclein, beta-amyloid (Aβ), and neurofibrillary tangle tau underlying the development of dementia symptoms in Parkinson' s disease.[13]

Until today, especially in developing countries, most of the diagnosis of Parkinson's disease was made from clinical symptoms. Meanwhile, these clinical symptoms will only appear when more than 60%–80% of the dopamine-producing cells in the substantia nigra are damaged.[14] This means that when the clinical diagnosis is made, the pathological conditions in the brains are already at an advanced stage. Measuring the Lewys body load in the brains of Parkinson's disease is a newer technique to determine how much brain damage has occurred, but this test is not yet available in all health facilities. Therefore, it is necessary to examine biomarkers, which are expected to be used as guidelines to suspect a pathological process in the patient's brain.

Biomarkers, such as alpha-synuclein, beta-amyloid, and tau protein, can be found in various body fluids, including cerebrospinal fluid, plasma, and serum, and even recently, their levels in saliva have also been developed for diagnostic purposes. Although the analysis of cerebrospinal liquor is better describe the levels of pathological fragments in the brain, however, taking a cerebrospinal fluid is classified as an invasive procedure. Thus, it is necessary to take alternative measures to obtain a pathological picture through plasma or serum body fluids. The purpose of this study was to assess the relationship between plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein with cognitive disorders in patients with Parkinson's disease.

Methods

Research design

A case-control design study was carried out on patients with Parkinson' s disease who were treated at referral hospital in West Sumatra Indonesia. The diagnosis of Parkinson' s disease was clinically established according to the criteria of the United Kingdom PD Society Brain Bank by a neurologist. Patients with any of the following symptoms were excluded from this study: atypical symptoms, secondary Parkinson' s, multiple system atrophy, corticobasal degeneration, post-stroke, and Parkinson' s due to the use of neuroleptic drugs. Up to 62 patients with Parkinson' s disease met the requirements, and all of these patients underwent a neuropsychological examination using the Montreal Cognitive Assessment Indonesian version

(MoCA-Ina). Also, 20 healthy adults were included in this study as controls. The degree of Parkinson' s disease was assessed using the Hoen and Yahr scale.

Cognitive function and staging examinations

The MoCA-Ina examination resulted in 40 patients with cognitive disorders (MoCA-Ina < 26) and 22 patients with normal cognitive function (MoCA-Ina ≥ 26). In the classification according to Hoen and Yahr scales, 8 patients were in Stadium; 15, in Stadium 2; 27, in Stage 3; 9, in Stage 4; and 3, in Stage 5. In this study, patients with Parkinson's disease were grouped into two disease stages, namely the mild stage (stages 1, 2, and 3 of Hoen and Yahr) and the severe stage (stages 4 and 5 Hoen and Yahr). The research protocol has passed the ethical clearance of the research ethics committee of the Faculty of Medicine, Andalas University, with No. 324/KEP/FK/2020.

Plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein examination

Examination of plasma beta-amyloid 42, alpha-synuclein, and tau protein was carried out by taking 5 cc of fasting venous blood into a vacutainer containing anticoagulants. The blood was then centrifuged at 2,000–3,000 rpm for 20 minutes, and the plasma was stored in a microtube at −80°C. After samples were collected, the examination of plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein were determined according to the manufacturer instructions of enzyme-linked immunoassay (ELISA) kits for humans from the Bioassay Technology Laboratory (BT Lab).

Statistical analysis

Statistical analysis was run using SPSS 21. The difference in average plasma levels of beta-amyloid, alpha-synuclein, and tau protein in the two groups (cognitive disorders and normal) was tested using the t-test if the data were normally distributed and the Mann–Whitney U test if they the data were abnormally distributed. The effect of confounding factors on cognitive disorders in both groups was tested using the chi-squared test.

Results

This research used 82 study subjects consisting of 62 patients with Parkinson's disease and 20 healthy adults as control of the same age and sex. The Parkinson's disease group consisted of 35 men and 27 women. The results of cognitive function examination using MoCA-Ina found 40 patients (64.5%) with impaired cognitive function and 22 people with normal cognitive function (Table 1). Based on Table 1, there was a relationship between the length of illness ($p = 0.036$) and disease stage ($p = 0.008$) with cognitive function.

Table 1. Clinical Characteristics of Research Subjects

Variable	Control (Healthy Adult) n = 20	Parkinson's Disease: Normal Cognitive n = 22	Parkinson's Disease: Impaired Cognitive n = 40	p	OR
Age					
≥65 years	11	10	22	0.475	1.467
<65 years	9	12	18		
Education					
≤12 years	10	10	24	0.271	1.8
>12 years	10	12	16		
Sex					
Man	10	15	20	0.192	0.46
Woman	10	7	20		
Disease Duration					
≥5 years	NA	4	18	0.036	3.682
<5 years	NA	18	22		
Disease Stage					
Severe	NA	9	30	0.008	4.333
Mild	NA	13	10		

It was found that plasma levels of beta-amyloid 42 in patients with Parkinson's disease were lower, but the other two parameters were higher compared to those in healthy adults (Table 2). The average plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein between patients with Parkinson's disease and the healthy adults were significantly different ($p < 0.05$).

Table 2. Differences in the Average Plasma Levels of Beta-amyloid 42, Alpha-synuclein, and Tau Protein in Healthy Adults and Patients with Parkinson's Disease

	Healthy Adults	Parkinson's Disease	p
Plasma Levels of Beta-amyloid 42 (ng/l)	347.8 (123.1–572.5)	121. 8 (76.4–167.2)	0.040*
Plasma Levels of Alpha-synuclein (ng/l)	199.5 (152.2–246.9)	396.2 (309.4–483.0)	0.034*
Plasma Levels of Tau Protein (ng/l)	110.9 (74.1–147.8)	198.0 (156.2–239.8)	0.033*

*Mann–Whitney U test

Next, the differences in plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein between groups with and without cognitive disorders were observed. Table 3 shows differences in beta amyloid 42 levels between groups with and without cognitive impairment ($p<0,05$), but no differences were found for level alpha synuclein and tau protein ($p>0,05$).

Table 3.Plasma Levels of Beta-amyloid 42, Alpha-synuclein, and Tau Protein in Groups With and Without Cognitive Disorders in ~~Patients with~~ Parkinson's Disease

Variable	Parkinson's Disease		
	With cognitive disorders n = 40	Without cognitive disorders n = 22	p
Level of Beta-amyloid 42 (ng/l)	74.58 (36.64–112.52)	207.60(22.50–715.58)	0.037*
Level of Alpha-synuclein (ng/l)	468.01(284.79–651.23)	356.68(262.68–450.68)	0.936*
Level of Tau Protein (ng/l)	244.88 (153.29–336.45)	172.23 (129.88–214.57)	0.27*

*Mann–Whitney U test

Discussion

Parkinson's disease has diverse neuropathological features that spread to almost all parts of the brain that occur in a chronically progressive manner. Clinically, patients with the disease were found to have various symptoms, both motoric and non-motoric, including cognitive disorders. It was reported that the cognitive disorder that appears in Parkinson's disease has a different pattern than in Alzheimer's disease. This is due to differences in the underlying neuropathological processes and the location of illness.[15]

There was no significant difference between the groups of patients with and without cognitive disorders regarding the distribution of age, education, and gender. However, the length and the stage of illness were significantly different between those two groups, in which patients with cognitive disorders had a longer illness duration and a more severe disease stage (Table 1). Parkinson's disease is a progressive chronic disease; this means that over time, the damage it causes will also increase. Thus, there is a relationship between the length of illness and the severity of the disease with the occurrence of cognitive dysfunction.

This study spotted a significance decrease in beta amyloid 42 (Aβ42) and an increase of alpha-synuclein and tau protein plasma level in patients with Parkinson's disease compared to control group of healthy adults. Various studies have shown that the main pathological feature in Parkinson's disease is the presence of alpha synuclein in the form ~~that forms~~ Lewy body aggregate proteins in neuronal cells.[16,17] However, others also reported that several pathological proteins are also involved in this disease, such as tau protein and beta-amyloid.[18,19] Some researchers state that plasma levels of alpha-synuclein in patients with Parkinson's disease are higher than those in healthy adults,[20,21] but Gorostidi[22] and Li QX[23] stated otherwise. A recent systematic review study and meta-analysis by Bougea A[24] noted that plasma alpha-synuclein levels are higher in people with Parkinson's disease while compared to healthy population. In this study, the plasma levels of alpha-synuclein in patients with Parkinson's disease were higher than those in the healthy adults (Table 2). By contrast, no difference in alpha-synuclein levels was found in the groups with and without cognitive disorders (Table 3).

The function of tau protein is to stabilize the microtubules of the cell membrane, but in pathological state, it will aggregate to form a neurofibrillary tangle (NFTs), known as tauopathy, which is the main sign of neurodegenerative diseases such as Alzheimer's and Parkinson's

diseases.[25,26] Based on previous studies, it is known that tau proteins (especially phosphorylated ones) are also found in Lewy bodies with alpha-synuclein, and NFT is also often seen around Lewy bodies.[27] These findings led to the conclusion that there is a positive interaction between the tau protein and alpha-synuclein. Until now, the relationship between tau protein and alpha synuclein iis still unknown with certainty. This study found that the plasma levels of tau protein in patients with Parkinson' s disease were higher than those in healthy adults (Table 2). Also, there was no difference in tau protein levels in the groups with and without cognitive disorders (Table 3).

In addition to the tau protein, the presence of beta-amyloid has also been associated with the pathological process of Parkinson' s disease, particularly cognitive disorders. Of the three forms of beta-amyloid isoforms (A β 38, A β 40, and A β 42) resulting from the breakdown of Amyloid Precursor Protein by beta and gamma secretase enzymes, the A β 42 isoform is the most toxic and tends to form aggregates, causing neuronal cell death and cognitive disorders.[28,29] According to the analysis of cerebrospinal fluid in patient with Parkinson's disease, it is known that there is an increase of alpha synuclein and tau protein, but it contradicts with the A β 42 levels.[30] A decrease in A β 42 levels in the cerebrospinal fluid indicates an impaired clearance of beta-amyloid in the brain so that the A β 42 levels in the brain increase. It was found that beta amyloid 42 levels were lower in people with Parkinson's disease than the healthy population and lower levels in the cognitive impaired than without cognitive impaired (table 3)

As the examination of cognitive function in this study used only MoCA-Ina and covered many domains, it would be remarkable if it was followed by other neuropsychological tests, such as the Clinical Dementia Rating, so that the level of cognitive disorders could be explored more. In addition, the number of samples included in this study is relatively small. Future research with a larger sample size with a cohort design is needed and is expected to further strengthen the results of this study.

Conclusion

The results of this study found that low plasma levels of beta-amyloid 42 (Aβ42) were associated with cognitive disorders in patients with Parkinson's disease.

Conflict of interest

There is no conflict of interest in this study.

Acknowledgment

The authors would like to thank the Faculty of Medicine, Andalas University, Padang for facilitating this research.

References

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Lampiran B

PROSES PEER REVIEW DALAM BENTUK *SUMMARY OF MODIFICATION*

Judul Artikel and	: Relationship between Plasma Level of Beta-amyloid, Alpha-synuclein Tau Protein with Cognitive Impairment in Parkinson disease
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Relationship between plasma level of beta-amyloid, alpha-synuclein and tau protein with cognitive impairment in Parkinson disease

Abstract

Background: Most people with Parkinson's disease will develop dementia along with their illness development. There are several overlapping brain pathological features in patients with Parkinson's and Alzheimer's disease. These features are related to beta-amyloid findings, alpha-synuclein, and tau protein.

Aim: This study was designed to determine the relationship between beta-amyloid, alpha-synuclein, and tau protein plasma level with cognitive impairment in Parkinson's disease.

Materials and Methods: This was observational with case-control design study. A total of 62 patients with Parkinson's disease and 20 healthy controls were included in this study. Parkinson's disease group was divided into 2 subgroups, patients with and without cognitive impairment based on Montreal Cognitive Assessment Indonesian version (MoCA-Ina) score. The plasma levels of beta-amyloid, alpha-synuclein, and tau protein were measured by using the enzyme-linked immunoassay technique. Student's t-test was used to analyze normally distributed data of plasma level differences between groups (Parkinson's disease group; control group) and subgroups (Parkinson disease with and without cognitive impairment). If the data was not normally distributed, the Mann-Whitney test was used. The level of significance was <0.05 (p-value <0.05).

Results: The result demonstrated significant differences in beta-amyloid, alpha-synuclein, and tau protein plasma level between Parkinson's disease and control group ($p<0.05$). We also found significant differences of beta-amyloid plasma level between Parkinson's with and without cognitive impairment subgroups ($p<0.05$), but none in other parameters ($p>0.05$).

Conclusion: Low plasma levels of beta-amyloid 42 (Aβ42) are associated with cognitive impairment in patients with Parkinson's disease.

Keywords: alpha-synuclein, beta-amyloid, cognitive impairment, Parkinson's disease, tau protein

Introduction

Along with the increasing life expectancy, degenerative diseases also show a significant rise in numbers. Parkinson's disease is one of the most common neurodegenerative disease, shows a similar pattern of increasing incidence. Parkinson's disease is known for its prominent motoric and non-motoric symptoms. Cognitive impairment is one of non-motoric symptoms that become the most debilitating symptom in Parkinson's disease development. People with Parkinson's disease have more than three to six times the risk to develop dementia than those of the same age without the disease [1], [2], [3]. Other reports suggest that the risk of dementia in Parkinson's disease is time-dependent. Its risk will increase along with the duration of Parkinson's disease. Cognitive impairment was found in 25% of cases at the beginning of Parkinson's disease and almost 80% will develop dementia over time [4], [5], [6].

The presence of alpha-synuclein in the brains of patients with Parkinson's disease is a major pathological finding and it can be found as Lewy bodies or Lewy neurites. However, from the immunohistochemical examination of this synuclein, it was also found in several cerebral cortex areas [7], [8], [9]. Postmortem studies also find amyloid plaques and neurofibrillary tangles in 30-40% Parkinson's patients' brain. This fact further convinces an overlapping pathological process between Parkinson's and Alzheimer's diseases and certainly influences the appearance of symptoms in patients [5], [10]. Several studies suspect a strong relation of pathological features of Alzheimer's disease with the appearance of cognitive disorders in Parkinson's disease [11], [12]. Research has found that the pathological combination of alpha-synuclein, beta-amyloid (Aβ), and neurofibrillary tangle tau have an important role in dementia development in Parkinson's disease [13].

Until today, especially in developing countries, most Parkinson's disease diagnosis is made from clinical symptoms. Meanwhile, these clinical symptoms will only appear when more than 60%–80% of the dopamine-producing cells in the substantia nigra are damaged [14]. This means that when the clinical diagnosis is made, the pathological conditions in the brains are already at an advanced stage. Nowadays, there are some updated techniques to diagnose Parkinson's disease by measuring Lewy body amount in the brain, but this test is not yet available in all health facilities. Moreover, there are not yet multicentric study regarding plasma biomarker, only a cross-sectional comparative study in control and Parkinson group, which reported the relationship between the low level of beta-amyloid and the high level of alpha synuclein and plasma T-Tau with cognitive impairment in Parkinson's [15]. Therefore, it is necessary to examine biomarkers, which are expected to be used as guidelines to suspect a pathological process in the patient's brain.

Biomarkers, such as alpha-synuclein, beta-amyloid, and tau protein, can be found in various body fluids, including cerebrospinal fluid, plasma, and serum, and even recently, their levels in saliva have also been developed in order to make the diagnosis [16]. Although the analysis of cerebrospinal liquor is better describing the levels of pathological fragments in the brain, however, taking a cerebrospinal fluid is classified as an invasive procedure. Thus, it is necessary to take alternative measures to obtain a pathological picture through plasma or serum body fluids. The purpose of this study was to assess the relationship between plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein with cognitive impairment in patients with Parkinson's disease.

Methods

Ethical clearance

The research protocol has passed the ethical clearance from the research ethics committee of the Faculty of Medicine, Andalas University, Indonesia, with registry number: 324/KEP/FK/2020.

Research design

A case-control design study was carried out on patients with Parkinson's disease who were treated at tertiary referral hospital in West Sumatra Indonesia. The diagnosis of Parkinson's disease was clinically established according to the criteria of the United Kingdom PD Society Brain Bank by a neurologist.

Patients with any of the following symptoms were excluded from this study: atypical symptoms, secondary Parkinson's, multiple system atrophy, cortico-basal degeneration, post-stroke, and Parkinson's due to the use of neuroleptic drugs. Up to 62 patients with Parkinson's disease met the requirements, and all these patients underwent a neuropsychological examination using the Montreal Cognitive Assessment Indonesian version (MoCA-Ina). Also, 20 healthy adults were included in this study as controls. The degree of Parkinson's disease was assessed using the Hoehn and Yahr scale.

Cognitive function and staging examinations

The MoCA-Ina examination resulted in 40 patients with cognitive impairment (MoCA-Ina < 26) and 22 patients with normal cognitive function (MoCA-Ina ≥ 26). In the classification according to Hoehn and Yahr scales, 8 patients were in Stage; 15, in Stage 2; 27, in Stage 3; 9, in Stage 4; and 3, in Stage 5. In this study, patients with Parkinson's disease were grouped into two disease stages, namely the mild stage (stages 1, 2, and 3 of Hoehn and Yahr) and the severe stage (stages 4 and 5 Hoehn and Yahr).

Plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein examination

The measurements of plasma beta-amyloid 42, alpha-synuclein, and tau protein were carried out by taking 5 cc of fasting venous blood into a vacutainer containing anticoagulants. The blood was then centrifuged at 2,000–3,000 rpm for 20 minutes, and the plasma was stored in a microtube at −80°C After samples were collected, the measurements of plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein were determined according to the manufacturer instructions of enzyme-linked immunoassay (ELISA) kits for humans from the Bioassay Technology Laboratory (BT Lab).

Statistical analysis

Statistical analysis was run using SPSS 21. The difference in average plasma levels of beta-amyloid, alpha-synuclein, and tau protein in the two groups (cognitive disorders and normal) was tested using the t-test if the data were normally distributed and the Mann–Whitney U test if the data were abnormally distributed. The effect of confounding factors on cognitive disorders in both groups was tested using the chi-squared test.

Results

This research used 82 study subjects consisting of 62 Parkinson's disease patients and 20 healthy controls in matched age and gender. The Parkinson's disease group consisted of 35 men and 27 women. The results of cognitive function examination using MoCA-Ina found 40 patients (64.5%) with impaired cognitive function and 22 people with normal cognitive function (Table 1). Based on Table 1, there was a relationship between the duration of illness ($p = 0.036$) and disease stage ($p = 0.008$) with cognitive function.

Table 1: Clinical characteristics of research subjects

Variable	Control (Healthy Adult) n = 20	Parkinson's Disease		p	OR
		Normal Cognitive n = 22	Impaired Cognitive n = 40		
Age					
≥65 years	11	10	22	0.475	1.467
<65 years	9	12	18		
Education					
≤12 years	10	10	24	0.271	1.8
>12 years	10	12	16		
Sex					
Man	10	15	20	0.192	0.46
Woman	10	7	20		
Disease Duration					
≥5 years	NA	4	18	0.036	3.682
<5 years	NA	18	22		
Disease Stage					
Severe	NA	9	30	0.008	4.333
Mild	NA	13	10		

It was found that plasma levels of beta-amyloid 42 in patients with Parkinson's disease were lower, but the other two parameters were higher compared to those in healthy adults (Table 2). The average plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein between patients with Parkinson's disease and the healthy adults were significantly different ($p < 0.05$).

Table 2: Differences in the average plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein in healthy controls and patients with Parkinson's disease

	Healthy Adults	Parkinson's Disease	p
Plasma Levels of Beta-amyloid 42 (ng/l)	347.8 (123.1–572.5)	121. 8 (76.4–167.2)	0.040*
Plasma Levels of Alpha-synuclein (ng/l)	199.5 (152.2–246.9)	396.2 (309.4–483.0)	0.034*
Plasma Levels of Tau Protein (ng/l)	110.9 (74.1–147.8)	198.0 (156.2–239.8)	0.033*

*Mann–Whitney U test

Next, the differences in plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein between subgroups with and without cognitive disorders. Table 3 shows significant differences in beta-amyloid 42 plasma levels between subgroups with and without cognitive impairment ($p<0.05$), but no significant differences were found for level alpha-synuclein and tau protein plasma level ($p>0.05$).

Table 3: Plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein in subgroups with and without cognitive impairment in Parkinson's disease

Variable	Parkinson's Disease		P
	With cognitive disorders n = 40	Without cognitive disorders n = 22	
Level of Beta-amyloid 42 (ng/l)	74.58 (36.64–112.52)	207.60(22.50–715.58)	0.037*
Level of Alpha-synuclein (ng/l)	468.01(284.79–651.23)	356.68(262.68–450.68)	0.936*
Level of Tau Protein (ng/l)	244.88 (153.29–336.45)	172.23 (129.88–214.57)	0.27*

*Mann–Whitney U test

Discussion

Parkinson's disease has diverse neuropathological features that spread to almost all parts of the brain that occur in a chronically progressive manner. Clinically, patients with the disease were found to have various symptoms, both motoric and non-motoric, including cognitive disorders. It was reported that the cognitive disorder in Parkinson's disease is not similar to the cognitive disorder found in Alzheimer's disease. This is due to differences in the underlying neuropathological processes and the location of illness [17].

There was no significant difference between the groups of patients with and without cognitive disorders regarding the distribution of age, education, and gender. However, the length and the stage of illness were significantly different between those two groups, in which patients with cognitive disorders had a longer illness duration and a more severe disease stage (Table 1). Parkinson's disease is a progressive chronic disease; this means that over time, it will cause an increase in the damage. Thus, there is a relationship between the length of illness and the severity of the disease with the occurrence of cognitive dysfunction.

This study spotted a significant decrease in beta-amyloid 42 (Aβ42) and an increase of alpha-synuclein and tau protein plasma levels in patients with Parkinson's disease compared to the control group of healthy adults. This study spotted a significant decrease in beta-amyloid 42 (Aβ42) and an increase of alpha-synuclein and tau protein plasma levels in patients with Parkinson's disease compared to the control group of healthy adults. This study spotted a significant decrease in beta-amyloid 42 (Aβ42) and an increase of alpha-synuclein and tau protein plasma levels in patients with Parkinson's disease compared to the control group of healthy adults.

Various studies have shown that the main pathological feature in Parkinson's disease is the presence of alpha-synuclein in the form of Lewy body aggregate proteins in neuronal cells [18], [19]. However, others also reported that several pathological proteins are also involved in this disease, such as tau protein and beta-amyloid [20,21]. Some researchers state that plasma levels of alpha-synuclein in patients with Parkinson's disease are higher than those in healthy adults [22], [23], but Gorostidi [24]

and Li [25] stated otherwise. A recent systematic review study and meta-analysis by Bougea [26] noted that plasma alpha-synuclein levels are higher in people with Parkinson's disease compared to the healthy population. In this study, it was found that plasma levels of alpha-synuclein in patients with Parkinson's disease were higher than those in healthy adults (Table 2). By contrast, no difference in alpha-synuclein levels was found in the groups with and without cognitive disorders (Table 3).

The function of tau protein is to stabilize the microtubules of the cell membrane, but in a pathological state, it will aggregate to form a neurofibrillary tangle (NFTs), known as tauopathy, which is the main key marker of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases [27], [28]. Based on previous studies, it is known that tau proteins (especially phosphorylated ones) are also found in Lewy bodies with alpha-synuclein, and NFT is also often seen around Lewy bodies [29]. These findings led to the conclusion that there is a positive interaction between the tau protein and alpha-synuclein. Until now, the relationship between tau protein and alpha-synuclein is not fully elucidated. This study found higher plasma levels of tau protein in patients with Parkinson's disease than those in healthy adults (Table 2). We also found no significant differences in tau protein levels between subgroups with and without cognitive impairment (Table 3).

In addition to the tau protein, the presence of beta-amyloid has also been associated with the pathological process of Parkinson's disease, particularly cognitive disorders. Of the three forms of beta-amyloid isoforms (Aβ38, Aβ40, and Aβ42) resulting from the breakdown of Amyloid Precursor Protein by beta and gamma secretase enzymes, the Aβ42 isoform is the most toxic and tends to form aggregates, causing neuronal cell death and cognitive disorders [30], [31]. According to cerebrospinal fluid analysis in patient with Parkinson's disease, it is known that there is an increase of alpha-synuclein, and tau protein, but it contradicts with the Aβ42 levels [32]. A decrease in Aβ42 levels in the cerebrospinal fluid indicates an impaired clearance of beta-amyloid in the brain so that the Aβ42 levels in the brain increase. It was found that beta-amyloid 42 levels were lower in people with Parkinson's disease than in healthy population (Table 2) and lower levels in the cognitively impaired than without cognitively impaired patients (Table 3).

As the examination of cognitive function in this study used only MoCA-Ina and covered many domains, it would be remarkable if it was followed by other neuropsychological tests, such as the Clinical Dementia Rating, so that the level of cognitive disorders could be explored more. In addition, the number of samples included in this study is relatively small. Future research with a larger sample size with a cohort design is needed and is expected to further strengthen the results of this study.

Conclusions

The results of this study found that low plasma levels of beta-amyloid 42 (Aβ42) were associated with cognitive impairment in patients with Parkinson's disease.

Acknowledgments

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Lampiran C

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Relationship between Plasma Level of Beta-amyloid, Alpha-synuclein, and Tau Protein with Cognitive Impairment in Parkinson Disease

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Abstract

BACKGROUND: Most people with Parkinson's disease will develop dementia, along with their illness development. There are several overlapping brain pathological features in patients with Parkinson's and Alzheimer's disease. These features are related to beta-amyloid findings, alpha-synuclein, and tau protein.

AIM: This study was designed to determine the relationship between beta-amyloid, alpha-synuclein, and tau protein plasma level with cognitive impairment in Parkinson's disease.

MATERIALS AND METHODS: This was observational with case–control design study. A total of 62 patients with Parkinson's disease and 20 healthy controls were included in this study. Parkinson's disease group was divided into two subgroups, patients with and without cognitive impairment based on Montreal Cognitive Assessment Indonesian version (MoCA-Ina) score. The plasma levels of beta-amyloid, alpha-synuclein, and tau protein were measured using the enzyme-linked immunoassay technique. Student's t-test was used to analyze normally distributed data of plasma level differences between groups (Parkinson's disease group; control group) and subgroups (Parkinson disease with and without cognitive impairment). If the data were not normally distributed, the Mann–Whitney U-test was used. The level of significance was < 0.05 ($p < 0.05$).

RESULTS: The result demonstrated significant differences in beta-amyloid, alpha-synuclein, and tau protein plasma level between Parkinson's disease and control group ($p < 0.05$). We also found significant differences of beta-amyloid plasma level between Parkinson's with and without cognitive impairment subgroups ($p < 0.05$), but none in other parameters ($p > 0.05$).

CONCLUSION: Low plasma levels of beta-amyloid 42 (Aβ42) are associated with cognitive impairment in patients with Parkinson's disease.

Introduction

Along with the increasing life expectancy, degenerative diseases also show a significant rise in numbers. Parkinson's disease is one of the most common neurodegenerative diseases, which shows a similar pattern of increasing incidence. Parkinson's disease is known for its prominent motoric and non-motoric symptoms. Cognitive impairment is one of non-motoric symptoms that become the most debilitating symptom in Parkinson's disease development. People with Parkinson's disease have more than 3–6 times the risk to develop dementia than those of the same age without the disease [1], [2], [3]. Other reports suggest that the risk of dementia in Parkinson's disease is time-dependent. Its risk will increase, along with the duration of Parkinson's disease. Cognitive impairment was found in 25% of cases at the beginning of Parkinson's disease and almost 80% will develop dementia over time [4], [5], [6].

The presence of alpha-synuclein in the brains of patients with Parkinson's disease is a major pathological finding and it can be found as Lewy bodies or Lewy neurites. However, from the immunohistochemical examination of this synuclein, it was also found in several cerebral cortex areas [7], [8], [9]. Postmortem studies also find amyloid plaques and neurofibrillary tangles in 30–40% Parkinson's patients' brain. This fact further convinces an overlapping pathological process between Parkinson's and Alzheimer's diseases and certainly influences the appearance of symptoms in patients [5], [10]. Several studies suspect a strong relation of pathological features of Alzheimer's disease with the appearance of cognitive disorders in Parkinson's disease [11], [12]. Research has found that the pathological combination of alpha-synuclein, beta-amyloid (Aβ), and neurofibrillary tangle tau has an important role in dementia development in Parkinson's disease [13].

Until today, especially in developing countries, most Parkinson's disease diagnosis is made from clinical symptoms. Meanwhile, these clinical symptoms will only appear when more than 60%–80% of the dopamine-producing cells in the substantia nigra are damaged [14]. This means that when the clinical diagnosis is made,

the pathological conditions in the brains are already at an advanced stage. Nowadays, there are some updated techniques to diagnose Parkinson's disease by measuring Lewy body amount in the brain, but this test is not yet available in all health facilities. Moreover, there is not yet multicentric study regarding plasma biomarker, only a cross-sectional comparative study in control and Parkinson group, which reported the relationship between the low level of beta-amyloid and the high level of alpha-synuclein and plasma T-Tau with cognitive impairment in Parkinson's [15]. Therefore, it is necessary to examine biomarkers, which are expected to be used as guidelines to suspect a pathological process in the patient's brain.

Biomarkers, such as alpha-synuclein, beta-amyloid, and tau protein, can be found in various body fluids, including cerebrospinal fluid, plasma, and serum, and even recently, their levels in saliva have also been developed to make the diagnosis [16]. Although the analysis of cerebrospinal liquor is better describing the levels of pathological fragments in the brain; however, taking a cerebrospinal fluid is classified as an invasive procedure. Thus, it is necessary to take alternative measures to obtain a pathological picture through plasma or serum body fluids. The purpose of this study was to assess the relationship between plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein with cognitive impairment in patients with Parkinson's disease.

Methods

Ethical clearance

The research protocol has passed the ethical clearance from the Research Ethics Committee of the Faculty of Medicine, Andalas University, Indonesia, with registry number: 324/KEP/FK/2020.

Research design

A case–control design study was carried out on patients with Parkinson's disease who were treated at tertiary referral hospital in West Sumatra Indonesia. The diagnosis of Parkinson's disease was clinically established according to the criteria of the United Kingdom PD Society Brain Bank by a neurologist. Patients with any of the following symptoms were excluded from this study: Atypical symptoms, secondary Parkinson's, multiple system atrophy, corticobasal degeneration, post-stroke, and Parkinson's due to the use of neuroleptic drugs. Up to 62 patients with Parkinson's disease met the requirements, and all these patients underwent a neuropsychological examination using the Montreal Cognitive Assessment Indonesian version (MoCA-Ina). Furthermore, 20 healthy adults were included in this study as controls. The degree of Parkinson's disease was assessed using the Hoehn and Yahr scale.

Cognitive function and staging examinations

The MoCA-Ina examination resulted in 40 patients with cognitive impairment (MoCA-Ina < 26) and 22 patients with normal cognitive function (MoCA-Ina ≥ 26). In the classification according to Hoehn and Yahr scales, eight patients were in Stage; 15, in Stage 2; 27, in Stage 3; 9, in Stage 4; 3, and in Stage 5. In this study, patients with Parkinson's disease were grouped into two disease stages, namely, the mild stage (Stages 1, 2, and 3 of Hoehn and Yahr) and the severe stage (Stages 4 and 5 Hoehn and Yahr).

Plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein examination

The measurements of plasma beta-amyloid 42, alpha-synuclein, and tau protein were carried out by taking 5 cc of fasting venous blood into a vacutainer containing anticoagulants. The blood was then centrifuged at 2,000–3,000 rpm for 20 mins, and the plasma was stored in a microtube at −80°C. After samples were collected, the measurements of plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein were determined according to the manufacturer instructions of enzyme-linked immunoassay (ELISA) kits for humans from the Bioassay Technology Laboratory (BT Lab).

Statistical analysis

Statistical analysis was run using SPSS 21. The difference in average plasma levels of beta-amyloid, alpha-synuclein, and tau protein in the two groups (cognitive disorders and normal) was tested using the t-test if the data were normally distributed and the Mann–Whitney U-test if the data were abnormally distributed. The effect of confounding factors on cognitive disorders in both groups was tested using the Chi-squared test.

Results

This research used 82 study subjects consisting of 62 Parkinson's disease patients and 20 healthy controls in matched age and gender. The Parkinson's disease group consisted of 35 men and 27 women. The results of cognitive function examination using MoCA-Ina found 40 patients (64.5%) with impaired cognitive function and 22 people with normal cognitive function (Table 1). Based on Table 1, there was a relationship between the duration of illness ($p = 0.036$) and disease stage ($p = 0.008$) with cognitive function.

Table 1: Clinical characteristics of research subjects

Variable	Control (healthy adult) (n = 20)	Parkinson's disease		p	OR
		Normal cognitive (n = 22)	Impaired cognitive (n = 40)		
Age (years)					
≥ 65	11	10	22	0.475	1.467
< 65	9	12	18		
Education (years)					
≤ 12	10	10	24	0.271	1.8
> 12	10	12	16		
Sex					
Man	10	15	20	0.192	0.46
Woman	10	7	20		
Disease duration (years)					
≥ 5	NA	4	18	0.036	3.682
< 5	NA	18	22		
Disease stage					
Severe	NA	9	30	0.008	4.333
Mild	NA	13	10		

OR: Odds ratio, NA: Not available.

It was found that plasma levels of beta-amyloid 42 in patients with Parkinson's disease were lower, but the other two parameters were higher compared to those in healthy adults (Table 2). The average plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein between patients with Parkinson's disease and the healthy adults were significantly different ($p < 0.05$).

Table 2: Differences in the average plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein in healthy controls and patients with Parkinson's disease

Indicators	Healthy adults	Parkinson's disease	p
Plasma levels of beta-amyloid 42 (ng/l)	347.8 (123.1–572.5)	121. 8 (76.4–167.2)	0.040*
Plasma levels of alpha-synuclein (ng/l)	199.5 (152.2–246.9)	396.2 (309.4–483.0)	0.034*
Plasma levels of tau protein (ng/l)	110.9 (74.1–147.8)	198.0 (156.2–239.8)	0.033*

*Mann–Whitney U-test.

Next, the differences in plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein between groups with and without cognitive disorders were determined. Table 3 shows significant differences in beta-amyloid 42 plasma levels between subgroups with and without cognitive impairment ($p < 0.05$), but no significant differences were found for level alpha-synuclein and tau protein plasma level ($p > 0.05$).

Table 3: Plasma levels of beta-amyloid 42, alpha-synuclein, and tau protein in subgroups with and without cognitive impairment in parkinson's disease

Variable	Parkinson's disease		p
	With cognitive disorders (n = 40)	Without cognitive disorders (n = 22)	
Level of beta-amyloid 42 (ng/l)	74.58 (36.64–112.52)	207.60 (22.50–715.58)	0.037*
Level of alpha-synuclein (ng/l)	468.01 (284.79–651.23)	356.68 (262.68–450.68)	0.936*
Level of tau protein (ng/l)	244.88 (153.29–336.45)	172.23 (129.88–214.57)	0.27*

*Mann–Whitney U-test.

Discussion

Parkinson's disease has diverse neuropathological features that spread to almost all parts of the brain that occurs in a chronically progressive manner. Clinically, patients with the disease were found to have various symptoms, both motoric and non-motoric, including cognitive disorders. It was reported that the cognitive disorder in Parkinson's disease is not similar to the cognitive disorder found in Alzheimer's disease. This is due to differences in the underlying neuropathological processes and the location of illness [17].

There was no significant difference between the groups of patients with and without cognitive disorders regarding the distribution of age, education, and gender. However, the length and the stage of illness were significantly different between those two groups, in which patients with cognitive disorders had a longer illness duration and a more severe disease stage (Table 1). Parkinson's disease is a progressive chronic disease; this means that over time, it will cause an increase in the damage. Thus, there is a relationship between the length of illness and the severity of the disease with the occurrence of cognitive dysfunction.

This study spotted a significant decrease in beta-amyloid 42 (Aβ42) and an increase of alpha-synuclein and tau protein plasma levels in patients with Parkinson's disease compared to the control group of healthy adults. This study spotted a significant decrease in beta-amyloid 42 (Aβ42) and an increase of alpha-synuclein and tau protein plasma levels in patients with Parkinson's disease compared to the control group of healthy adults. This study spotted a significant decrease in beta-amyloid 42 (Aβ42) and an increase of alpha-synuclein and tau protein plasma levels in patients with Parkinson's disease compared to the control group of healthy adults.

Various studies have shown that the main pathological feature in Parkinson's disease is the presence of alpha-synuclein in the form of Lewy body aggregate proteins in neuronal cells [18], [19]. However, others also reported that several pathological proteins are also involved in this disease, such as tau protein and beta-amyloid [20], [21]. Some researchers state that plasma levels of alpha-synuclein in patients with Parkinson's disease are higher than those in healthy adults [22], [23], but Gorostidi [24] and Li [25] stated otherwise. A recent systematic review study and meta-analysis by Bougea [26] noted that plasma alpha-synuclein levels are higher in people with Parkinson's disease compared to the healthy population. In this study, it was found that plasma levels of alpha-synuclein in patients with Parkinson's disease were higher than those in healthy adults (Table 2). By contrast, no difference in alpha-synuclein levels was found in the groups with and without cognitive disorders (Table 3).

The function of tau protein is to stabilize the microtubules of the cell membrane, but in a pathological state, it will aggregate to form a

neurofibrillary tangles (NFTs), known as tauopathy, which is the main key marker of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases [27], [28]. Based on previous studies, it is known that tau proteins (especially phosphorylated ones) are also found in Lewy bodies with alpha-synuclein, and NFT is also often seen around Lewy bodies [29]. These findings led to the conclusion that there is a positive interaction between the tau protein and alpha-synuclein. Until now, the relationship between tau protein and alpha-synuclein is not fully elucidated. This study found higher plasma levels of tau protein in patients with Parkinson's disease than those in healthy adults (Table 2). We also found no significant differences in tau protein levels between subgroups with and without cognitive impairment (Table 3).

In addition to the tau protein, the presence of beta-amyloid has also been associated with the pathological process of Parkinson's disease, particularly cognitive disorders. Of the three forms of beta-amyloid isoforms (Aβ38, Aβ40, and Aβ42) resulting from the breakdown of Amyloid Precursor Protein by beta and gamma secretase enzymes, the Aβ42 isoform is the most toxic and tends to form aggregates, causing neuronal cell death and cognitive disorders [30], [31]. According to cerebrospinal fluid analysis in patient with Parkinson's disease, it is known that there is an increase of alpha-synuclein, and tau protein, but it contradicts with the Aβ42 levels [32]. A decrease in Aβ42 levels in the cerebrospinal fluid indicates an impaired clearance of beta-amyloid in the brain so that the Aβ42 levels in the brain increase. It was found that beta-amyloid 42 levels were lower in people with Parkinson's disease than in healthy population (Table 2) and lower levels in the cognitively impaired than without cognitively impaired patients (Table 3).

As the examination of cognitive function in this study used only MoCA-Ina and covered many domains, it would be remarkable if it was followed by other neuropsychological tests, such as the clinical dementia rating so that the level of cognitive disorders could be explored more. In addition, the number of samples included in this study is relatively small. Future research with a larger sample size with a cohort design is needed and is expected to further strengthen the results of this study.

Conclusion

The results of this study found that low plasma levels of beta-amyloid 42 (Aβ42) were associated with cognitive impairment in patients with Parkinson's disease.

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