



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

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Abstract

Edited by: Branislav Filipović

Citation: Syafrita Y, Istarini A, Busra M, Indra S, Susanti R. Relationship Between Plasma Level of Beta-amyloid, Alpha-synuclein, and Tau Protein with Cognitive Impairment in Parkinson Disease. Open Access Maced J Med Sci. 2022 Mar 15; 10(B):663-667. <https://doi.org/10.3889/oamjms.2022.7940>

Keywords: Alpha-synuclein; Beta-amyloid; Cognitive impairment; Parkinson's disease; Tau protein

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Received: 12-Nov-2021

Revised: 28-Feb-2022

Accepted: 05-Mar-2022

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Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

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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-Ind) 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 $p < 0.05$ ($p < 0.05$).

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 (A β 42) 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 (A β), 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-I_{na}). 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-I_{na} examination resulted in 40 patients with cognitive impairment (MoCA-I_{na} < 26) and 22 patients with normal cognitive function (MoCA-I_{na} ≥ 26). In the classification according to Hoehn and Yahr scales, eight patients were in Stage 1; 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-I_{na} 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 (A β 42) 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 (A β 42) 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 (A β 42) 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 (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 [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 A β 42 levels [32]. 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 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 (A β 42) were associated with cognitive impairment in patients with Parkinson's disease.

Acknowledgments

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

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