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RESEARCH ARTICLE

Association between Serum Alpha-Synuclein Levels and Parkinson's Disease Stage

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's. It is chronically progressive with the main symptoms of resting tremor, rigidity, bradykinesia, and postural disturbances. Lewy's body and Lewy's neurite are the main findings in brain biopsies of patients with PD. The main component is alpha-synuclein, a misfolding protein that plays an essential role in the pathogenesis of PD. This study aims to determine the association between serum alpha-synuclein levels during the PD stage and compare the levels between PD patients and healthy populations of the same age. A case-control study was conducted on 62 people with PD and 20 normal subjects as controls in the outpatient Department of Neurology of Dr. M. Djamil General Hospital and Ibnu Sina Islamic Hospital, Padang, from March to September 2020. The ELISA method examined serum alpha-synuclein examination, and the PD stage was assessed according to Hoehn and Yahr stages. The differences in alpha-synuclein levels between cases and controls and between stages of PD were analyzed by the Mann-Whitney test. Alpha-synuclein levels in PD patients were higher than in controls, and this difference was statistically significant ($p<0.05$). On the other hand, alpha-synuclein levels were higher in the severe stage than in the mild stage but not statistically significant ($p>0.05$). In conclusion, there was no association between alpha-synuclein levels and the stage of Parkinson's disease. Still, serum alpha-synuclein levels in PD patients were significantly higher than in the healthy population.

Keywords: Alpha-synuclein, Hoehn and Yahr stage, Parkinson's disease

Introduction

Along with the increase in life expectancy, the incidence of neurodegenerative diseases also increases, one of which is currently in the spotlight of the medical world is Parkinson's disease (PD). The disease affects up to 2% of the population aged >65 years and >3% of the population 80 years. The symptoms are resting tremor, rigidity, and bradykinesia, responsive to the administration of levodopa.[1] In America, about 60,000 new cases are reported every year. Parkinson's disease (PD) occurs due to the degeneration of dopamine-producing neurons in the midbrain, precisely in the substantia nigra pars compacta.[2] PD can significantly affect a person's quality of life, especially motor symptoms such as stiffness and tremors, cognitive decline, and depression can also occur.[3]

Alpha-synuclein is a protein thought to be essential for the pathogenesis of PD, although the mechanism by which this protein causes neurotoxicity and degeneration is not fully understood.[4] Alpha-synuclein is a protein that forms energy in cells that makes our brains work. For each protein to function correctly, it must be folded into the correct shape. In healthy brain cells, normal alpha-synuclein is usually found right on the surface of the membranes surrounding the cell body and at the ends of branches extending from the cell (presynaptic terminals) that are important for relaying messages between neurons.[5] However, in PD, some alpha-synuclein proteins were found to be folded in the wrong way. This incorrectly constructed version of alpha-synuclein then clumps together with other pathological proteins to form the aggregates we call Lewy's bodies. Lewy bodies are especially abundant in areas of the brain that have experienced cell loss, such as areas containing dopamine neurons.[6,7]

The main pathological feature of PD is the finding of the pathological protein alpha-synuclein in the form of Lewy's bodies and Lewy's neurites in cells of the central nervous system. Until recently, especially in developing countries, most diagnoses of PD were made from clinical symptoms. However, we know that

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these symptoms will only appear when more than 60–80% of the dopamine-producing cells in the substantia nigra are damaged.[8] It means that when a clinical diagnosis is made, the pathological conditions in the brains of people with PD are already severe. In this regard, we are interested in examining serum alpha-synuclein levels associated with the clinical stage of PD and comparing their levels with the normal population.

Methods

An observational study with a case-control design was carried out on PD patients treated at the outpatient Department of Neurology of Dr. M. Djamil General Hospital and Ibnu Sina Islamic Hospital, Padang, from March to September 2020. The research protocol has passed the ethical approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Andalas, Padang, with registry number: 355/UN.16.2/KEP-FK/2021. The diagnosis of PD was made clinically according to the criteria of the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB)[9] by a neurologist. Patients with atypical symptoms, secondary Parkinson's, multiple systemic atrophy, corticobasal degeneration, post-stroke, and Parkinson's due to the use of neuroleptic drugs were excluded.

We got 62 patients with PD who met the requirements, and all of these patients were examined for serum alpha-synuclein levels and the clinical stage of PD.

According to Hoehn and Yahr stage, in this study, patients with PD were only grouped into two stages of the disease, namely mild stage (stages 1, 2, and 3) and severe stage (stages 4 and 5). Alpha-synuclein levels were checked by ELISA method using enzyme-linked immunoassay kits for humans from the Bioassay Technology Laboratory (BT Lab). SPSS version 22.0 was used for statistical analysis. The average difference in serum alpha-synuclein levels at mild and severe stages and between cases and controls was tested using a t-test if the data were normally distributed and a Mann-Whitney test if the data distribution was not normal. In addition, the effect of confounding factors on the disease stage was tested with the chi-square test.

Results

The data on the characteristics of the research subjects can be seen in Table 1. There were 82 study subjects consisting of 62 PD patients and 20 healthy adult controls of the same age and gender. The cases of PD consisted of 35 men and 27 women. From the stadium examination, it was found that stage 1 with 8 people, stage 2 with 15 people, stage 3 with 27 people, stage 4 with 9 people, and stage 5 with 3 people.

The basic data for age, gender, and level of education between the severe and mild stage groups with PD patients were relatively equal, which was indicated by a p value>0.05, but for the length of illness, there was a significant difference

Table 1 Characteristics of Respondents

Variables	Healthy Adult Control (n=20)	Parkinson's Disease		p*	OR
		Severe Stage (n=12)	Mild Stage (n=50)		
Age (years old)					
≥65	11	9	37	0.944	1.05
<65	9	3	13		
Education (years)					
≤12	10	4	19	0.766	0.82
>12	10	8	31		
Gender					
Men	10	6	29	0.619	0.73
Women	10	6	21		
Duration of illness (years)					
≥5	NA	8	14	0.013	5.14
<5	NA	4	36		

Note: *chi-square test

with a p value=0.013, where the duration of illness in the severe stage group is longer than the mild stage group.

The bivariate analysis of differences in alpha-synuclein levels between the case and control groups (healthy population) can be seen in Table 2. Alpha-synuclein levels in the case group were higher than in the control group and this difference was statistically significant with a p value=0.034.

The difference in the average levels of groups with severe and mild stages can be seen in Table 3. Alpha-synuclein levels in the severe stage were higher than in the mild stage, but this difference was not statistically significant with a p value=0.323.

Discussion

The study aims to analyze the serum alpha-synuclein levels of PD patients and compare them with the normal population of the same age. It also analyses the association between serum alpha-synuclein levels and the stage of PD. The study involved 62 PD patients and 20 healthy adults as a control group. Out of the 62 PD patients, there were more males than females with a ratio of 1.48:1. It is similar to other studies that PD affects males 1.5–2 times more often than females.[10–13] However, the mortality rate and speed of disease progression are higher in women than in men.

Most (80.6%) PD patients who participated in this study were in stages 1, 2, and 3 Hoehn and Yahr (mild stage), and the others were in stages 4 and 5 (severe stage). There is a significant association between length of illness and disease stage. Parkinson's disease patients in the severe stage group suffer longer (≥5 years) than those in the mild stage group. Parkinson's disease patients who have suffered from this disease for five years have a 5.14 times risk of being in a severe stage compared to PD patients who have suffered less than five years. Parkinson's disease is a chronic progressive disease that will continue to get worse over time. Moreover, many studies state that when PD symptoms appear, the damage to dopamine-producing cells in the substantia nigra pars compacta is more than 60%, where this damage continues. Thus with increasing time, the patient's clinical stage will be more severe.

Alpha-synuclein levels were found to be higher in PD patients than in the healthy population (control), and the difference was statistically significant ($p<0.05$). Also, serum alpha-synuclein levels were higher in the severe stage group than in the mild stage group, although this difference was not statistically significant ($p>0.05$). Alpha-synuclein is one of the pathological proteins that co-forms Lewy's bodies and Lewy's neurite (LB and LN) along with other pathological proteins. On autopsy examination of the brain of patients with PD, there were pigmented areas in the substantia nigra of the midbrain. It microscopically corresponds to the neuromelanin dopaminergic neurons of the substantia nigra pars compacta.[15,16] Eosinophilic inclusions (5–30 in diameter) can also be found in the soma neurons that are still intact. Lewy's bodies

Table 2 Differences in Alpha-Synuclein Levels between Case and Control Groups

	Healthy Control (n=20)	Parkinson's Disease (n=62)	p
Alpha-synuclein level (ng/L)	199.5 (152.2–246.9)	396.2 (309.4–483.0)	0.034*

Note: *Mann-Whitney test

Table 3 Differences in Alpha-Synuclein Levels between Severe and Mild Parkinson's Disease Groups

	Parkinson's Disease		p
	Severe Stage (n=12)	Mild Stage (n=50)	
Alpha-synuclein level (ng/L)	275.76 (91.95–1,260.69	226.73 (50.71–1,318.53)	0.323*

Note: *Mann-Whitney test

and Lewy's neurite were seen alive in routine histopathological staining.[15–17]

Although alpha-synuclein is the dominant protein in LB and LN, other proteins such as ubiquitin, neurofilament protein, ubiquitin-binding protein p62, tubulin, and synphilin-1 are also present in the structure.[15–18] The results of this study are similar to a study by Chang et al.,[19] which reported increased peripheral circulating (plasma and serum) alpha-synuclein levels in PD compared to age-matched health and found an association between serum alpha-synuclein levels and clinical disease severity. Other studies have also observed increased alpha-synuclein levels in the plasma of PD patients compared to controls, but the associated parameters vary variably.[20–23] However, several other studies found decreased alpha-synuclein levels in the plasma of PD patients compared to controls, and there was no significant difference in this parameter between the two groups.[19,24] Thus, although peripheral alpha-synuclein (serum or plasma) is considered a promising candidate biomarker, the present study results are inconsistent. It is due to several things that are difficult to avoid, such as the various stages of disease and duration of illness of PD patients included in the study. In addition, most studies are still in the cross-sectional method, and the control group included in the study is almost always normal subjects.

Conclusions

There is no association between serum alpha-synuclein levels in Parkinson's disease patients with the stage of the disease. However, the alpha-synuclein levels were higher in patients with Parkinson's disease than in healthy individuals.

Conflict of Interest

There is no conflict of interest in this research.

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