Plasma tau protein and A β 42 level as markers of cognitive impairment in patients with Parkinson's disease

Justyna Chojdak-Łukasiewicz^{1,A,B,D}, Małgorzata Małodobra-Mazur^{2,C},
Anna Zimny^{3,C}, Leszek Noga^{4,C}, Bogusław Paradowski^{1,A,F}

¹ Department of Neurology, Wrocław Medical University, Poland

² Department of Forensic Medicine, Molecular Techniques Unit, Wrocław Medical University, Poland

³ Department of General Radiology, Interventional Radiology and Neuroradiology, Wrocław Medical University, Poland

⁴ Department of Pathophysiology, Wrocław Medical University, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;

D – writing the article; E – critical revision of the article; F – final approval of the article

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Address for correspondence

Justyna Chojdak-Łukasiewicz

E-mail: justyna.ch.lukasiewicz@gmail.com

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Abstract

Background. Parkinson's disease (PD) is a progressive neurodegenerative disorder with a characteristic clinical picture. Apart from classical movement disorders, a significant role is also played by non-motor symptoms, in particular cognitive impairments, which have a significant impact on the quality of life of the patients. Tau protein and amyloid beta are well-known non-specific biomarkers in Alzheimer's disease (AD).

Objectives. The study assessed the practical value of determining tau protein and amyloid beta (A β 42) in the blood serum of patients with PD and their relationship with cognitive impairments, radiographic image and the used dose of L-DOPA.

Material and methods. The neuropsychological assessment was carried for 64 patients with PD. The levels of amyloid beta 1–42 (A β 42) and tau proteins in serum were also measured.

Results. The A β 42 level in the serum was statistically higher in patients with longer duration of the disease ($p < 0.05$) and those who were taking a higher dose of L-DOPA ($p < 0.05$). The average level of tau protein in the serum was slightly lower in the study groups than in the control group and showed no statistical significance. No correlation was found between the levels of tau protein and A β 42 and the results of neuropsychological tests. Tau protein correlated with hippocampal atrophy ($p < 0.05$).

Conclusions. Serum levels of A β 42 and tau protein in PD may be a useful marker for the assessment of cognitive impairments. The role of L-DOPA in the process of dementia in PD remains unclear.

Key words: Parkinson's disease, dementia, amyloid β -protein, tau protein

Cite as

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease with a characteristic clinical picture.¹ An important role in PD is played by non-motor symptoms.² Special significance is given to cognitive disturbances, which can evolve to mild cognitive impairment (MCI) or dementia. Dementia in PD occurs in about 40% of patients and the risk of cognitive disorders in this group is about 6 times greater than in the general population and increases with the duration of the disease.³ The search continues for specific biomarkers for PD in body fluids. Currently, tests include determination of the levels of alpha-synuclein (ASN), uric acid, DJ-1, amyloid beta, tau protein, epidermal growth factor (EGF), and glutathione.⁴ In the case of Alzheimer's disease (AD), amyloid beta and tau protein are well-established biomarkers. A change in their levels permits a diagnosis of AD with high sensitivity and specificity (90–95%), also during the preclinical period.⁵

This study aimed to assess the practical value of the levels of tau protein and amyloid beta (Aβ42) in the blood serum of PD patients with symptoms of cognitive disorders of varying degrees of severity, including the duration of the disease and the applied dose of L-DOPA, and to determine whether these proteins can be a markers of neurodegenerative changes in PD.

Methods

Subjects

The study group (group I) comprised 64 patients (29 women, 35 men) with an established diagnosis of idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria, divided into 2 subgroups according to the disease duration: up to 5 years (group IA) and over 5 years (group IB). The majority of the patients (42 cases) were hospitalized at the Clinic of Neurology of the University Hospital in Wrocław, Poland, whereas the other subjects consisted of outpatients. All patients provided written informed consent for participation in the study. The control group (group C) was matched by sex and age with the patients and consisted of 30 healthy volunteers without evidence of cognitive impairment, extrapyramidal syndrome or neurological deficit in neurological examination.

Measures of clinical symptoms

The following data was collected for all patients: demographic data, general medical history, history of the disease, history of previous treatment, history of comorbidities, and assessment of the neurological status. In PD patients, the total applied dose of L-DOPA was calculated.

The main purpose of this study required the use of only the five-point Hoehn and Yahr scale (H–Y) to assess the degree of motor disability in the PD group.^{1,6}

Neuropsychological assessment

Cognitive functions were examined with the use of neuropsychological tests: Mini-Mental State Examination (MMSE) and the Clock Drawing Test (CDT) which is recognized worldwide as a neuropsychological screening tool. One of the most frequently used methods of CDT scoring is the Sunderland et al. version. A part of the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog test) assessing the ability to remember a list of words ("word recall"), and a verbal fluency test (Controlled Oral Word Association Test – COWAT) in the alphabet-phonemic category (COWATf) and the semantic category (COWATs) consisting of "fruit and vegetables." The obtained results were referred to the standards set for each age group and gender of the studied patients. Depressive disorders were excluded in all subjects examined using the Beck Depression Inventory (BDI).

Neuroradiological assessment

Seven PD patients were evaluated neuroradiologically using computed tomography (CT) because of contraindications to magnetic resonance imaging (MRI). The remaining patients underwent MRI. The degree of hippocampal atrophy was assessed using the Scheltens rating scale between 0 and 4 to evaluate atrophy of the hippocampus, parahippocampal gyrus, entorhinal cortex, and surrounding cerebrospinal fluid (CSF) on coronal reconstructions,^{7,8} where the following degrees of the scale meant:

- 0 – no atrophy,
- 1 – only widening of choroid fissure,
- 2 – also widening of temporal horn of lateral ventricle,
- 3 – moderate loss of hippocampal volume (decrease in height), and
- 4 – severe volume loss of hippocampal volume.

Cortical atrophy was assessed with respect to frontal, frontotemporal, parietal, and occipital lobe regions, and within the brainstem using the visual rating scale scoring between 0 and 3,^{7,8} where the following degrees of the scale meant:

- 0 – no cortical atrophy,
- 1 – mild atrophy,
- 2 – moderate atrophy, and
- 3 – severe atrophy.

Assessment of subcortical atrophy included the presence of a widened ventricular system and vasogenic lesions (on a scale of 0–3, where 0 means no lesions of this type).

Plasma tau and Aβ42 measurements

Ten milliliters of native peripheral blood samples were collected from each PD patient and each

subject in group C; the samples were then centrifuged at 2,000 g for 10 min. Pure serum was drained and frozen in test tubes at -80°C . The samples were thawed just before determination of the levels of tau protein and A β 42. Tau protein and A β 42 levels were assessed using the High Sensitivity Human Amyloid β 42 ELISA kit (Merck Millipore, Burlington, USA) and the Invitrogen Human Tau (Total) ELISA kit (Invitrogen, Carlsbad, USA). The substance levels were determined using enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. Both kits used specific monoclonal antibodies that recognized a particular epitope within tau protein or amyloid beta. In the next stage of the reaction, streptavidin conjugated with horseradish peroxidase was added, marking appropriate, specific antibody-antigen complexes. After the tracer solution was added, the contents of the sample changed color if tau protein or amyloid beta were present. The process of color reaction was inhibited by the addition of sulfuric acid, which was expressed by another color change. The color intensity of the solution was measured in a spectrophotometer at 450 nm. The sensitivity threshold was 16 pg/mL in the case of A β 42 and 12 pg/mL in the analysis of tau protein.

Statistical analysis

All statistical analyses were performed with STATISTICA v. 10 PL software (StatSoft Inc., Tulsa, USA). We first assessed the normality assumption of all variables by using the Kolmogorov–Smirnov test. If normal distribution was confirmed, the data was presented as mean with standard deviation (SD). The results in both groups (I vs C) were then compared using Student's t-test. Correlation was assessed using Pearson's correlation coefficient. Analysis of variance (ANOVA) with Scheffe's post hoc test was used to compare more than 2 group means (IA vs IB vs C). In the absence of normal distribution, medians and percentiles were calculated and group comparisons were made using the Kruskal–Wallis test, while Spearman's rank correlation coefficient was used to determine whether correlations exist. The significance threshold was set at $p < 0.05$.

Results

Table 1 shows the demographic characteristics, mean levels of A β 42 and tau protein, and results obtained in neuropsychological tests and BDI in the study groups.

Table 1. Demographic and clinical characteristics and levels of A β 42 and tau in patients with PD and controls

Variable	Group I (n = 64)	Group IA (n = 32)	Group IB (n = 32)	Control group (C) (n = 30)	I vs C P (t-test)	IA vs IB vs C P (ANOVA)
Age	68.3 $\pm$ 9.8 (44–87)	69.0 $\pm$ 10.0	67.6 $\pm$ 9.7	64.8 $\pm$ 9.5	0.1 (NS)	0.24
Sex (M/F)	35/29	11/21	24/8	15/15	0.67 (χ^2 test)	0.005 (χ^2 test)
Duration of illness [years]	6.2 $\pm$ 4.6	2.7 $\pm$ 1.6	9.6 $\pm$ 3.9	–	–	–
H–Y scale	2.8 $\pm$ 0.8	2.5 $\pm$ 0.8	3.1 $\pm$ 0.8	–	–	0.002 (IA vs IB)
MMSE	27.2 $\pm$ 2.3	27.2 $\pm$ 2.2	27.2 $\pm$ 2.4	28.5 $\pm$ 1.7	0.01	0.03
MMSE men	27.2 $\pm$ 2.6 (n = 35)	26.2 $\pm$ 2.4 (n = 11)	26.9 $\pm$ 2.4 (n = 24)	28.6 $\pm$ 1.5 (n = 15)		0.03 (IA vs C)
MMSE cor	27.2 $\pm$ 2.1	27.3 $\pm$ 2.0	27.0 $\pm$ 2.2	28.2 $\pm$ 1.6	0.02	0.05 (NS)
CDT	8.0 $\pm$ 2.0	8.1 $\pm$ 1.8 *	7.9 $\pm$ 2.1 *	9.3 $\pm$ 1.4	0.001	0.004
CDT men	8.2 $\pm$ 2.1 (n = 35)	7.6 $\pm$ 2.2 (n = 11)	7.8 $\pm$ 2.1 (n = 24)	9.3 $\pm$ 1.4 (n = 15)	–	0.03 (IB vs C)
COWATs	16.1 $\pm$ 5.7	16.8 $\pm$ 5.4	15.3 $\pm$ 6.0	18.6 $\pm$ 5.7	0.049	0.08
COWATs men	16.0 $\pm$ 6.2 (n = 35)	14.3 $\pm$ 5.2 (n = 11)	14.7 $\pm$ 6.2 (n = 24)	19.4 $\pm$ 5.4 (n = 15)	–	0.03 (IB vs C)
COWATf	12.0 $\pm$ 4.7	11.7 $\pm$ 4.9	12.3 $\pm$ 4.5	11.3 $\pm$ 4.3	0.5	0.71
ADAS-cog	16.4 $\pm$ 5.1	16.8 $\pm$ 3.7	16.0 $\pm$ 6.1	18.1 $\pm$ 4.4	0.12	0.23
Beck	8.1 $\pm$ 2.2	7.9 $\pm$ 2.3 *	8.4 $\pm$ 2.1 *	5.9 $\pm$ 3.5	0.001	0.001
Beck men	6.9 $\pm$ 2.9 (n = 35)	7.0 $\pm$ 2.6 (n = 11)	8.25 $\pm$ 2.1 (n = 24)	4.9 $\pm$ 3.4 (n = 15)	–	0.002 (IB vs C)
A β 42 [pg/mL]	12.1 $\pm$ 12.6	8.5 $\pm$ 10.9	15.8 $\pm$ 13.3**	26.0 $\pm$ 64.4	0.56 (Scheffe's test)	0.006 (IB vs C)
Tau [pg/mL]	20.1 $\pm$ 15.7	20.9 $\pm$ 19.9	19.2 $\pm$ 10.1	21.4 $\pm$ 13.3	0.82	–

Values expressed as mean $\pm$ SD. * analyzed group vs control <0.05 (Scheffe's test); ** group IB vs control $p < 0.05$ (according to the Kruskal–Wallis test); NS – nonsignificant; ANOVA – analysis of variance; M – male; F – female; H–Y scale – Hoehn and Yahr scale; MMSE – Mini-Mental State Examination; MMSE cor – correlation of Mini-Mental State Examination; CDT – Clock Drawing Test; COWATf – Controlled Oral Word Association Test in the alphabetic-phonemic category; COWATs – Controlled Oral Word Association Test in the semantic category; ADAS-cog – Alzheimer's Disease Assessment Scale–Cognitive Subscale; A β 42 – amyloid beta 42.

There were no differences between the groups in terms of age ($p > 0.05$). Patients with longer disease duration had statistically significantly higher scores on the H-Y scale. The mean dose of the used L-DOPA was 673 mg/day in the whole group, 463 mg/day in the IA group, and 884 mg/day in the IB group.

A statistically significant difference was identified in MMSE and its adjusted value between group I and group C ($p < 0.05$). Also, a statistically significant MMSE difference was identified between the group of male patients with shorter disease duration and the males from group C. No significant correlation was found between the groups IA, IB, and group C (Scheffe's test). In the CDT test, the mean score for the whole group I was statistically significantly lower compared to group C. Scheffe's comparison test also showed statistical significance between the groups IA, IB, and group C. The scores obtained in the verbal fluency test in the semantic category were statistically significantly lower ($p < 0.05$) in group I compared to group C. Male patients with longer disease duration obtained statistically lower scores in the semantic category of the verbal fluency test than the other males. No statistical significance was found in the other groups. There were no significant differences in verbal fluency results in the phonetic category or the ADAS-cog test (all $p > 0.05$). Statistically significantly higher scores on the BDI scale were obtained in the whole group of PD patients (group I) and in the Scheffe's comparative test between the study subgroups (IA and IB). Also, male patients

with longer disease duration had statistically significantly higher scores on the BDI scale than the other males. No differences were observed between females.

The median test showed differences indicating a statistically higher level of Aβ42 in the IB group; 75% of the value was greater than the total median ($p < 0.05$). The mean level of tau protein in the blood serum in the study groups was slightly lower than in group C and showed no statistical significance. Fifteen patients in group I showed an elevated level of tau protein and a decreased level of Aβ42 as in the case of AD.

Table 2 shows Spearman's rank correlation coefficient, which revealed no significant correlations between the level of Aβ42; the mean scores of MMSE, MMSE correlation (MMSE cor), CDT, COWATf, COWATs, and ADAS-cog; and the mean score on the BDI scale (all $p > 0.05$). In the group of patients with a higher mean dose of L-DOPA, there was a significantly higher level of Aβ42 ($r = 0.043$; $p = 0.013$). In the case of tau protein, no correlation was found with neuropsychological tests, the BDI scale, and the used mean dose of L-DOPA in Spearman's rank correlation (all $p > 0.05$).

Atrophy of the hippocampus (changes ≥ 1 on the Schellens's scale) was found in 46 patients (71%), predominantly on the right side. In the IA subgroup, hippocampal atrophy occurred in 21 patients (69%), with a slight prevalence on the right side. In the IB subgroup, it occurred in 25 patients (78%) and manifested symmetrically. Cortical atrophy affected mostly frontal and temporal lobes

Table 2. Correlation between neuropsychological tests and Aβ42 and tau protein level

Aβ42						
Variable	Group I		Group IA		Group IB	
	Spearman's r	p-value	Spearman's r	p-value	Spearman's r	p-value
MMSE	0.0262	0.8367	−0.0438	0.8115	0.0984	0.5920
MMSE cor	−0.0374	0.7691	0.0068	0.9702	0.0043	0.9811
CDT	0.0250	0.8441	0.1157	0.5282	−0.1302	0.4773
COWATf	0.0201	0.8745	0.0714	0.6975	−0.2192	0.2279
COWATs	0.0596	0.6395	0.1795	0.3254	−0.0063	0.9724
ADAS-cog	−0.0179	0.8882	0.2051	0.2599	−0.1336	0.4658
Beck	−0.1504	0.2353	−0.2345	0.1963	−0.1355	0.4594
Tau protein						
MMSE	0.0581	0.648	−0.0047	0.980	0.184	0.313
MMSE cor	0.106	0.404	0.0425	0.818	0.2317	0.202
CDT	0.1366	0.282	0.1833	0.315	0.0788	0.668
COWATf	−0.0235	0.854	−0.1265	0.490	0.2043	0.262
COWATs	0.0655	0.607	−0.0105	0.954	0.1923	0.291
ADAS-cog	−0.087	0.494	−0.184	0.313	−0.0136	0.941
Beck	−0.1219	0.337	−0.1988	0.275	0.049	0.790

Values expressed as mean $\pm$ SD. * analyzed group vs control < 0.05 (Scheffe's test); ** group IB vs control $p < 0.05$ (according to the Kruskal-Wallis test); NS – nonsignificant; MMSE – Mini-Mental State Examination; MMSE cor – correlation of Mini-Mental State Examination; CDT – Clock Drawing Test; COWATf – Controlled Oral Word Association Test in the alphabetic-phonemic category; COWATs – Controlled Oral Word Association Test in the semantic category; ADAS-cog – Alzheimer's Disease Assessment Scale–Cognitive Subscale.

Table 3. The location of brain atrophy and vascular changes in PD

Group IA						
Score	FA	TA	PA	BA	SA	VCh
0	13	8	13	29	14	17
1	16	22	17	3	12	10
2	3	2	2	0	6	3
3	0	0	0	0	0	2
Group IB						
0	9	4	7	23	12	16
1	14	23	21	8	10	11
2	7	4	4	1	10	4
3	2	1	0	0	0	1

PD – Parkinson's disease; FA – frontal atrophy; TA – temporal atrophy; PA – parietal atrophy; BA – brainstem atrophy; SA – subcortical atrophy; Vch – vascular change.

and had a low degree of severity (mostly grade 1 atrophy). Cerebellar atrophy was reported in 30 patients and brainstem atrophy was found in 12 patients. There were no cases with identified atrophy of the occipital area. There were 38 patients with grade 1 and 16 patients with grade 2 (moderate) subcortical atrophy. Vascular changes were present in 31 PD patients (48%). The results are presented in Table 3. The level of A β 42 in the serum did not correlate with any of the evaluated parameters in neuroimaging studies ($p > 0.05$). The level of tau protein only correlated with hippocampal atrophy ($r = -0.3096$, $p = 0.013$).

Discussion

In the conducted study, the mean level of A β 42 protein was significantly higher in the blood serum in the group with longer disease duration (IB) than in the IA group and the control group. The level of tau protein was lower than in group C and showed no statistical significance in the respective groups. The level of A β 42 in the serum did not correlate with any of the evaluated parameters in neuroimaging studies. The level of tau protein only correlated with hippocampal atrophy. No correlation was found between, on the one hand, tau protein and A β 42 and, on the other hand, the results of neuropsychological tests and BDI. Only in 15 patients from the entire group I the absolute levels of A β 42 and tau protein behaved as in the CSF in AD.⁵

Literature data mainly concerns determination of A β 42 and tau protein in body fluids of AD patients, although attempts are being made to determine both those substances in PD patients. Authors of studies on the levels of A β 42 and tau protein in the CSF hold different opinions on the applicability of their research to PD and PD with dementia (PD-D). Some of the authors found no differences in the levels of A β 42 and tau protein in the CSF of PD patients compared to controls. Montine et al.⁹ determined the levels of A β 42, tau protein, and its phosphorylated form

phospho-tau (P181-Tau) in the CSF in patients with PD and PD-D, noting a lowered level of amyloid beta with normal or low levels of tau protein. Alves and Shi^{10,11} showed decreased levels of tau protein and its phosphorylated form in the CSF. A study by Leverenz et al.¹² involving a group of 22 patients with PD without cognitive disorders, analyzed results of neuropsychological tests and the levels of A β 42, tau protein, and brain-derived neurotrophic factor (BDNF) in the CSF. A relationship was found between the levels of A β 42, BDNF, and A β 42/t-tau and the mean scores in neuropsychological tests. No correlation was found with the level of tau protein. The authors suggest the coexistence of the AD mechanism underlying dementia in PD. Similar results were obtained in a prospective study of 45 patients, which showed a link between a decreased level of A β 42 in the CSF and the progression of cognitive decline without finding such relationship in the case of tau protein and its phosphorylated form.¹³ A study of 48 patients with PD of varying degrees of severity found an elevated level of tau protein and tau/A β 42 ratio in the CSF.¹⁴ The A β 42 and tau protein determined in the CSF are not unique to AD; they can also be markers of cognitive decline and clinical progression in PD-D.

Data relating to the determination of A β 42 and tau protein in the serum is limited. The A β 42 level in the serum shows diverse and ambiguous behavior. Alzheimer's disease shows normal, increased, or decreased levels of A β 42.^{15–17} The observed differences in peripheral blood may be due to external factors, including the collection time and storage conditions of the blood samples.¹⁸ The level of A β 42 may depend on the drugs used and the degree of atrophy of medial structures of the temporal lobe. An elevated level of A β 42 in the serum was found in cases of a genetically determined, familial form of AD, associated with mutations in the presenilin or *APP* genes and in the case of trisomy of chromosome 21.¹⁹ Drugs that may affect the levels of A β 40 and A β 42 include, among others, calcium channel blockers, digitalis preparations, anticoagulants, antipsychotics, insulin, and other hypoglycemic agents. It is believed that L-DOPA used in the treatment of PD may also have an effect. Our research has demonstrated that the mean daily dose of L-DOPA has a significant impact on the increased level of A β 42 in the serum. In the case of levodopa, the route of administration of the drug may be important. L-DOPA is absorbed after oral administration in the small intestine by active transportation along the pathway of macromolecular neutral amino acids. Its absorption is subject to fluctuations because of competitive displacement by amino acids from foods, such as phenylalanine, leucine and valine. Other possible influences include disorders of peristalsis, changes in the movement of material from the stomach to the small intestine, intestinal barrier impairment, or activation of immune mechanisms. Blasko et al.,²⁰ while analyzing the levels of A β 42 in a group of 526 people over the age of 75 without cognitive impairment, found a correlation between the levels of A β 42

and age. Similar results were obtained in the assessment of the levels of Aβ40 and Aβ42 in the serum depending on the age in AD, MCI and PD.²¹ The Framingham Heart Study²² found a link between lower levels of Aβ42 in the serum and a higher risk of developing AD in more than 2,000 patients over 60 years of age without dementia. No such relationship was found in the case of Aβ40. Different results were obtained in the Cardiovascular Health Study,²³ where the levels of Aβ40 and 42 in the serum increased with age in 274 people over 70 years of age. However, no relationship was found between the level of Aβ in the serum and the risk of developing AD. Studies by Hansson et al. and van Oijen et al.^{24,25} showed that an increased level of Aβ40, a decreased level of Aβ42, and a decreased level of the Aβ42:Aβ40 ratio were associated with a higher risk of dementia in people over 70 years of age. A meta-analysis of 13 studies found that a reduction of the Aβ42:Aβ40 ratio in the serum was associated with a higher risk of developing AD.²⁶ A change in the levels of Aβ42 and Aβ40 in the serum and the CSF was reported in the case of depressive disorders. Patients with diagnosed depression exhibit a lower level of Aβ42 in the CSF and the serum and an increase in the Aβ 40:Aβ 42 ratio in the serum.²⁷ Researchers also noted elevated levels of Aβ42 in the serum of patients with chronic kidney disease, correlating with eGFR.²⁸ These observations seem to indicate that chronic renal failure may be an independent risk factor for the development of dementia.²⁹ Tau protein levels in the serum are characterized by high variability and range from <10 pg/mL to >1,000 pg/mL while the gradient of tau protein between the CSF and the serum is 10:1.³⁰ The level of tau protein in the serum may be significantly lower than in the CSF. Higher concentration of the analyzed material may increase its detectability. The level of detection of tau protein in the serum depends on the sensitivity of the ELISA method and the used monoclonal antibodies. The level of tau protein may also be affected by enzymatic modifications leading to separation of epitopes detected with the used monoclonal antibody. Detectability of tau protein may be weakened by the serum presence of proteins that are homogeneous in relation to tau protein (e.g., MAP4 protein). Tau protein may also come from dorsal root ganglia, which has no clinical significance.³¹ Hattori et al. determined the level of tau protein in the oral epithelium in AD patients and concluded that it was higher than in the control group.³² Ingelson et al. found no significant difference between the levels of tau protein in the serum of PD patients and the control group.³³

Our research has shown that levels of Aβ42 and tau protein in the serum of PD patients are highly variable and do not correlate with the mean scores in the tests used to evaluate the severity of cognitive disorders and cannot be markers of neurodegenerative changes in PD with cognitive impairment. The dose of the used L-DOPA may have a negative impact on the level of Aβ42 in PD, but its role in the process of PD dementia remains unclear.

ORCID iDs

Justyna Chojdak-Łukasiewicz <https://orcid.org/0000-0002-0777-4565>
 Małgorzata Małodobra-Mazur <https://orcid.org/0000-0002-9864-5928>
 Anna Zimny <https://orcid.org/0000-0001-6214-0322>
 Bogusław Paradowski <https://orcid.org/0000-0003-2940-380X>

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