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Comparative Analysis Of Serum Alpha-Synuclein Levels In Parkinson's Disease And Essential Tremor Groups

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Abstract
***Introduction**: Parkinson's disease (PD) and essential tremor (ET) are common movement disorders with overlapping symptoms such as tremor. However, their pathophysiological mechanisms differ. PD is a neurodegenerative disorder associated with alpha-synuclein accumulation, while ET is characterized by motor dysfunction without confirmed neurodegeneration. This study investigates serum alpha-synuclein levels as a biomarker for differentiating PD and ET.*
***Methods**: The study included 111 participants divided into three groups: 31 PD patients (mean age: 58.71±10.81 years), 50 ET patients (mean age: 42.36±14.90 years), and 30 healthy controls (mean age: 40.80±12.90 years). Serum alpha-synuclein levels were measured using ELISA. Statistical analysis included ANOVA, t-tests, and correlation analysis (significance level:* $p < 0.05$*).*
***Results**: Serum alpha-synuclein levels were significantly higher in PD (754.64±105.8 pg/mL) compared to ET (711.05±173.5 pg/mL) and controls (13.9±9.4 pg/mL) (*$p < 0.001$*). ET patients also exhibited elevated alpha-synuclein levels relative to controls, suggesting early neurodegenerative processes. PD was associated with acute progression, while ET showed chronic progression with longer disease duration. A history of ET was noted in 19% of PD patients, indicating a potential link between the disorders.*
***Discussion**: Elevated alpha-synuclein levels in PD confirm its role as a biomarker of neurodegeneration. While ET patients showed lower levels than PD, their elevation suggests possible early neurodegeneration. These findings highlight alpha-synuclein's potential for differential diagnosis. Study limitations include small sample size and lack of long-term follow-up.*
***Conclusion**: Serum alpha-synuclein is a promising biomarker for distinguishing PD and ET. Future research should explore multi-biomarker panels and longitudinal assessments to enhance diagnostic accuracy.*
***Keywords**: Parkinson's disease, essential tremor, alpha-synuclein, biomarkers, early diagnosis, neurodegenerative disorders, risk factors, comparative analysis*

INTRODUCTION

Parkinson's disease (PD) and essential tremor (ET) are among the most common movement disorders in the world. Both are manifested by tremor, i.e. involuntary twitching of muscle movements. However, it is important to distinguish the pathophysiological basis and clinical features of PD and ET, as the clinical implications and treatment strategies of these disorders differ dramatically [7,11,22].

PD is essentially a neurodegenerative disease caused by the loss of dopamine-producing neurons in the brain. The main feature of this disease is the pathogenic accumulation of the protein alpha-synuclein. Quantification of this protein and its plasma levels are being investigated as a biomarker for early detection and diagnosis of PD.

Essential tremor is a non-neurodegenerative disease characterised predominantly by movement disorders, the role of alpha-synuclein in its pathogenesis is poorly understood [14,19].

Recent studies have focused on serum alpha-synuclein levels. Different studies have reported different levels of alpha-synuclein in PD, suggesting its association with neurodegenerative processes. Until now, neuroscientists have said that the amount of alpha-synuclein in ET is low and the disease is not neurodegenerative. Therefore, analysing alpha-synuclein levels may be an important tool to identify clinical differences between PD and ET [5,9,10,23].

In neurodegenerative diseases such as Parkinson's disease (PD) and essential tremor (ET), the study of serum alpha-synuclein levels is important in diagnostic and clinical studies. The use of biomarkers to detect differences between PD and ET is now widely considered [8,15].

Parkinson's disease and alpha-synuclein

The pathogenesis of PD is based on the accumulation of alpha-synuclein in Levi's corpuscles. According to a study by Albillos et al (2021), alpha-synuclein levels were higher in the PD group compared to the ET group and healthy individuals. Their results confirm that the elevation of alpha-synuclein in PD is associated with its accumulation in neurons. Work by Shu and colleagues (2018) also suggests that elevated serum alpha-synuclein levels can be used as a biomarker of PD [6,8,16].

Essential tremor and alpha-synuclein

Studies of alpha-synuclein levels in ET continue to show mixed results. Bain et al (2017) show that alpha-synuclein levels were higher in the ET group than in healthy controls, but lower than in the PD group. These results may suggest that ET has the initial stages of neurodegenerative processes. According to a study by Shill et al (2020), low levels of alpha-synuclein in ET reflect pathophysiological processes related to its characteristic of tremor [9,12,20,21].

Levels of alpha-synuclein in healthy subjects

In healthy individuals, serum alpha-synuclein levels were consistent with the physiological state. According to Beach et al (2010), alpha-synuclein levels reflect dynamics without a decrease in physiological values. Their results confirm that alpha-synuclein is maintained at low levels in serum under normal conditions [1.9.17].

The aim of this study is to investigate the amount of alpha-synuclein in the serum of PD and ET patients and healthy controls, to analyse the differences between them and to evaluate the relationship between age and alpha-synuclein levels. The results may help to improve the clinical diagnosis process and distinguish between PD and ET.

MATERIALS AND METHODS

A total of 111 participants were included in the study and were divided into Parkinson's disease (PD) patients, essential tremor (ET) patients and healthy subjects. Thirty-one patients participated in the PD group, with a mean age of 58.71±10.81 years. Fifty patients participated in the ET group, with a mean age of 42.36±14.90 years. The healthy control group consisted of 30 participants, with a mean age of 40.80±12.90 years. Written informed consent was obtained from all participants, and the study was conducted in accordance with international bioethical guidelines. Participants in all groups were comparable in age, sex, and clinical characteristics.

Table 1. Mean age and standard deviation in the groups of patients with Parkinson's disease, essential tremor and healthy subjects

Group	Quantity	Mean age (year)	Standard deviation (year)
Parkinson's disease	31	58.71	10.81
Essential tremor	50	42.36	14.90
Healthy	30	40.80	12.90

The diagnosis of Parkinson's disease was confirmed based on clinical guidelines. In the PD group, motor function of patients was assessed using UPDRS (Unified Parkinson's Disease Rating Scale). The diagnosis of essential tremor was established according to clinical guidelines based on postural tremor of the hands and other extremities. The level of tremor was assessed using the TETRAS (essential tremor rating scale). It was confirmed that participants in the healthy control group did not have motor and neurological disorders.

The amount of alpha-synuclein in serum was determined in all groups by ELISA (enzyme-linked immunosorbent assay). Blood samples were collected according to standard protocols and stored at -80°C. An ELISA kit for human alpha-synuclein was used to determine alpha-synuclein levels. All analyses were performed according to the manufacturer's instructions.

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Statistical analysis in the study was performed using SPSS 26.0 software. Differences between groups were evaluated using analysis of variance (ANOVA). T-test was used to identify differences between the two groups. Correlation analysis was performed to assess the relationship between age, disease duration and alpha-synuclein levels. In all tests, the level of statistical significance was taken as $p<0.05$.

RESULTS AND DISCUSSION

In patients with Parkinson's disease (PD), the mean stage on the Hen and Yahr scale was 1.84±0.63. The scores on this scale reflect the different stages of the disease in patients. According to the analysis, 6 patients with PD had a history of essential tremor (ET). Of these: in 2 patients ET was present since childhood, in 2 patients since adolescence, and in 2 patients since middle age. These results support the hypothesis of a clinical and pathophysiological relationship between PD and ET. The presence of ET in the patients' history suggests that it may influence the likelihood of PD in the future.

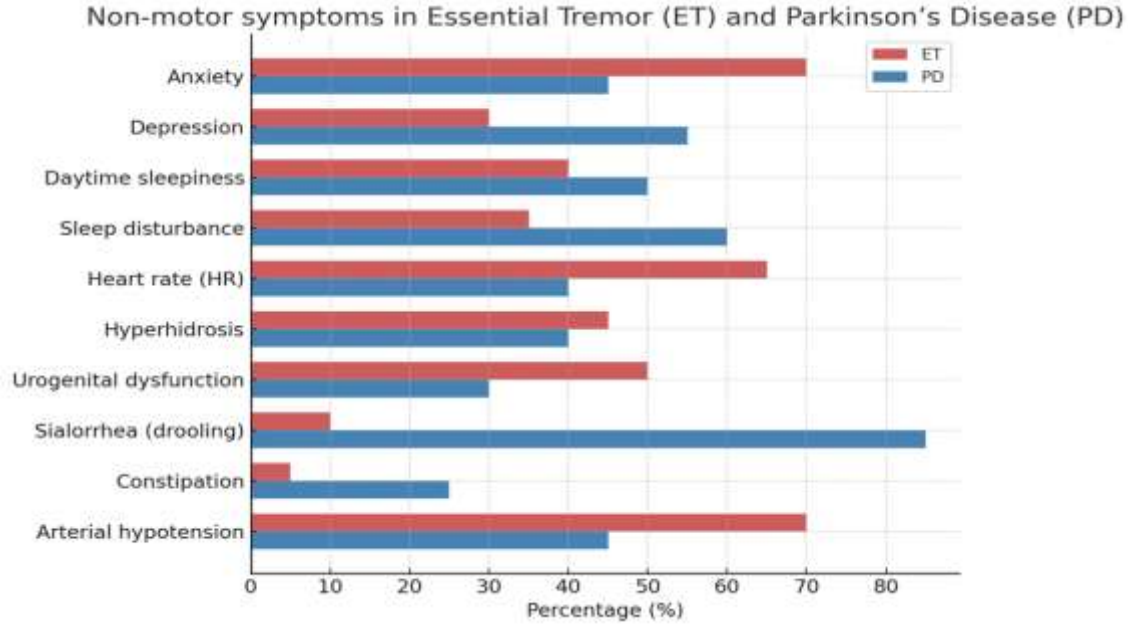

Figure 1: Comparative analysis of autonomic symptoms in patients with PD and ET.

The chart presents data on patients with two different diseases, PD (Parkinson's disease) and ET (essential tremor), and the presence of various clinical symptoms. These symptoms include depression and anxiety, arterial hypotension or orthostatic hypotension, salivation, constipation, urinary disturbances, generalised hyperhidrosis, heart rate (HR), sleep disturbances and daytime sleepiness. In the PD group, arterial hypotension or orthostatic hypotension was observed in 45% of patients, whereas in the ET group it was observed in only 78% of patients.Salivation occurred in 23% of PD patients and 2% of ET patients. Constipation was reported in 84% of PD patients and 20% of ET patients. Urinary disturbances were noted in 29% of patients with PD and 44% of patients with ET. Generalised hyperhidrosis was observed in 35% of patients with PD and 42% of patients with ET. Changes in heart rate (HR) occurred in 32% of patients with PD and 68% of patients with ET. Sleep disturbances were reported in 64% of PD patients and 28% of ET patients. Data on depression and anxiety disorders show that 67% of PD patients had depression, while anxiety occurred in only 20% of patients. In contrast, in the ET group, depression was reported in 30% of patients and anxiety in 70%. Problems with daytime sleepiness in PD patients occurred in 52% of patients, while in the ET group this figure was 36%. These data allow us to conclude that Parkinson's disease is characterised by pronounced autonomic disorders (salivation, constipation, sleep disturbances, HR changes), as well as a high frequency of depression. Essential tremor is accompanied by marked anxiety, arterial hypotension and hyperhidrosis, which indicates the prevalence of autonomic dysfunction and emotional instability. These data can help in differential diagnosis and in choosing an individual approach to treatment aimed at correction of both motor, vegetative and emotional disorders.

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The values of disease duration in patients with Parkinson's disease (PD) and essential tremor (ET) were compared. Twenty-three of 31 PD patients had a disease debut of 1 to 5 years, this group representing 74.2% of patients. Patients with a duration of 5-10 years were 8, representing 25.8% of the total group. In PD patients, the duration of the disease ends in a relatively short time, and long-term cases are rare.

Table 2. Disease duration and distribution of patients with PD and ET.

Group	Duration (year)	Number of patients	Percentage
PD	1-5	23	74.2%
PD	6-10	8	25.8%
ET	1-5	11	22%
ET	6-10	12	24%
ET	10+	25	50%
ET	20+	6	12%
ET	30+	5	10%

In 50 patients with ET, the duration of the disease was significantly longer. In 11 patients with ET the disease was observed in terms of 1 to 5 years (22%), and in 12 patients (24%) - with a duration of 6-10 years. The largest group had a follow-up period of more than 10 years; this group included 25 patients (50%). Of these 25 patients, 6 patients had disease duration of more than 20 years (12%) and 5 patients had disease duration of more than 30 years (10%). (Table 2.)

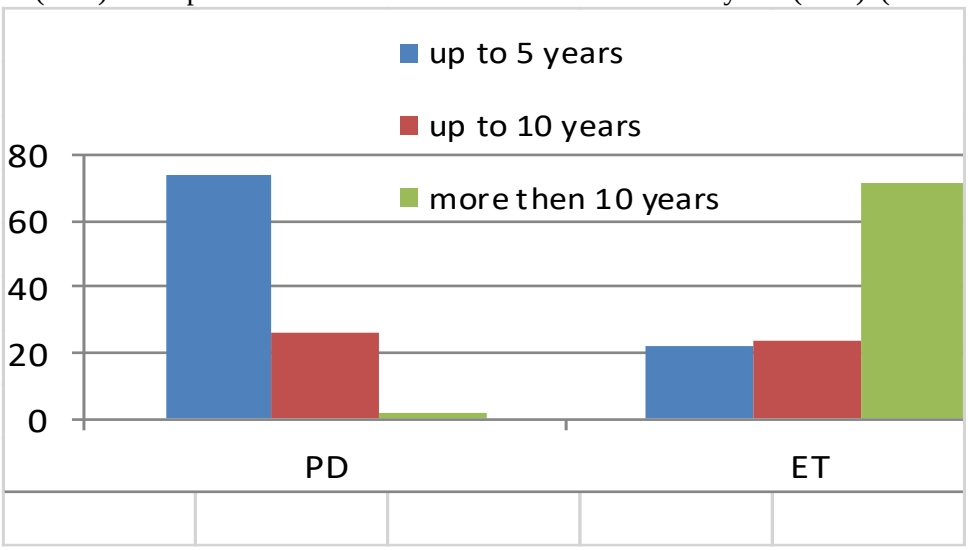

Figure 2: Disease duration and distribution of patients with PD and ET.

Significant differences in disease duration were found between PD and ET patients. The majority of PD patients had a short duration of onset and very few long-term cases. More remote cases were recorded in ET patients, indicating a greater identification of pathogenesis of a chronic nature. ANOVA analysis revealed statistically significant differences between groups ($p<0.01$). The longer duration indicates the evolution of the disease in patients with ET and possible difficulties in diagnosis. The results of the analyses are important for the development of disease management strategies and a better understanding of the clinical differences between ET and PD.

Six out of 31 patients with Parkinson's disease (PD) had a history of essential tremor (ET). Among the total number of PD patients, 2 patients (6.45%) had ET at a young age. The number of patients diagnosed with ET in adolescence was 2 (6.45%). In the remaining 2 patients (6.45%), ET occurred in middle age. These data show the prevalence of history of ET in PD patients. The occurrence of ET at different ages indicates that it influences the likelihood of developing PD at later stages. Larger analyses are needed to further explore the relationship between ET and PD among patients. These results provide a basis for a better understanding of the pathogenesis of neurodegenerative processes.

Clinical features in patients with essential tremor (ET) were analysed (Table 4). Alpha-synuclein levels in patients with PD (754.64 ± 105.8 pg/ml) and ET (711.05 ± 173.5 pg/ml) were significantly higher than in controls (13.9 ± 9.4 pg/ml), confirming its role in the pathogenesis of these diseases. PD is characterised by 100% tremor progression, resting tremor with plastic tone and high asymmetry (90%), which distinguishes it from ET (4%, 10%, 20%, respectively). In the ET group, 65% of patients have a history of ET (there is a hereditary aggravation, whereas in PD only 19%, indicating possible comorbidity or differences in aetiology. The majority of PD patients studied (74%) had a disease duration of 1-5 years, whereas in ET the predominant forms were long-standing: 50% had a history of ≥10 years, 12% had a history of ≥20 years, and 10% had a history of ≥30 years. The control group shows low alpha-synuclein values (median: 11.27 pg/ml), emphasising its non-specificity for neurodegenerative disorders. The variation of alpha-synuclein data is higher in ET (SD ±173.5) than in PD (±105.8), which may reflect the heterogeneity of essential tremor. Resting tremor and plastic tone were detected in 5 patients (10%), and in these cases there was plastic rigidity between movements and resting hand tremor. Asymmetry was noted in 10 patients (20%), with tremor being strongly marked on one side. Analyses show differences between the clinical manifestations of asymmetry and tremor in the ET condition, confirming that it shares similar clinical features with Parkinson's disease. The progressive increase in tremor is mainly due to the dynamic development of the disease and the severe disruption of neuromotor connections. These data serve as a basis for a better understanding of individual and general manifestations of ET, identifying clinical differences in the diagnostic process.

Table 3. Alpha-synuclein levels in groups of patients with Parkinson's disease, essential tremor and controls

	PD	ET	Control group
N	31	50	30
Alfa sinuclein	754,64±105,8	711,05±173,5	13,9±9,4
Max	974	986,3	39,76
Min	535	14,3	7,35
Median	751	727,04	11,27

Serum alpha-synuclein levels were analysed in Parkinson's disease (PD), essential tremor (ET) and healthy control groups. The mean alpha-synuclein levels in the PD group were 754.64±105.8 pg/ml, the highest value was 974 pg/ml, the lowest value was 535 pg/ml, and the median value was 751 pg/ml. In the ET group, the alpha-synuclein level was 711.05±173.5 pg/ml, the highest value. 986.3 ng/ml, the lowest value was 14.3 pg/ml, the median value was 727.04 pg/ml. In the healthy control group, the mean alpha-synuclein level was 13.9±9.4 pg/ml, the highest value was 39.76 pg/ml, the lowest value was 7.35 pg/ml, and the median value was 11.27 pg/ml. Levels of alpha-synuclein in PD and ET groups were significantly higher than in the control group of healthy people ($p<0.001$).

Table 4. Biochemical and clinical characteristics of patients with Parkinson's disease, essential tremor and control group

Parameters	PD	ET	Control
N	31	50	30
Alpha-synuclein (pg/ml)	754.64 ± 105.8	711.05 ± 173.5	13.9 ± 9.4
M	974	986.3	39.76
м	535	14.3	7.35
Median	751	727.04	11.27
Tremor progression (%)	100%	4%	- -
Resting tremor and plastic tone (%)	100%	10%	- -
Asymmetry (%)	90%	20%	- -
History of ET cases (%)	19%	65%	- -

Duration 1-5 years (%)	74%	22%	- -
Duration 6-10 years (%)	26%	24%	- -
Duration 10+ years (%)	-	50%	- -
Duration 20+ years (%)	-	12%	- -
Duration 30+ years (%)	- -	10%	- -

Notes* PD - Parkinson's disease. MT - Essential tremor.M - mean value, m - minimum value.'-' - data are missing or not applicable.Percentages represent the proportion of patients with the indicated feature in the group.

The higher levels in the PD group may be related to the accumulation of alpha-synuclein in Levi's corpuscles. Levels in the ET group were lower than in the PD group, indicating that the intensity of the neurodegenerative process was lower than in PD. In healthy subjects, alpha-synuclein levels reflected normal physiological status. ANOVA analysis was performed to evaluate the differences between groups, the level of statistical significance was recorded as $p<0.001$. Alpha-synuclein levels were higher in the PD group, reflecting the intensity of the neurodegenerative processes. Levels in the ET group were also higher, indicating a possible initial neurodegenerative nature of the disease, but the intensity of the process was lower compared to PD.

The aim of this study is to investigate whether these disorders can be distinguished clinically by assessing serum alpha-synuclein levels in Parkinson's disease (PD), essential tremor (ET) and healthy subjects. According to the results, alpha-synuclein levels in the PD group were significantly higher than in the healthy control group, and values in the ET group also showed higher levels close to PD.

This suggests that this condition may be related to the accumulation of alpha-synuclein in Levi's corpuscles in PD, whereas in ET it may reflect early neurodegenerative processes. The similarity of the clinical features of ET and PD may cause difficulties in diagnosis. The analysis showed that although the difference in alpha-synuclein levels between the PD and ET groups was not statistically significant, higher levels were noted in the PD group. The fact that such differences were observed especially in the long-term course of the diseases indicates the intensity of neurodegenerative processes. These results confirm the importance of using alpha-synuclein as a biomarker in diagnosis. The fact that in ET patients the level of alpha-synuclein in remote cases, especially in cases with a duration of more than 20-30 years, is lower than in PD, suggests that this may be related to the intensity of the neurodegeneration process. In the healthy control group, the level of alpha-synuclein corresponded to the normal physiological state.

Anamnestic information is important to better understand the relationship between PD and ET. ET anamnesis appeared at different ages in PD patients, and this may provide new information in understanding the mechanism of neurodegenerative processes. The results suggest that ET has important symptoms supporting the possibility of clinical transition to PD.

There are limitations of this study, which are mainly related to the limited number of groups and the lack of long-term dynamic follow-up data. However, the results of this study show promise for the use of alpha-synuclein as a biomarker in diagnosis.Future studies should aim to further explore differences between groups, develop multi-component biomarker panels for diagnosis, and expand data on the dynamics of alpha-synuclein levels.

Serum alpha-synuclein levels may provide an opportunity to improve the diagnostic process in distinguishing PD from ET. The valuable results of the study help to reduce the difficulties in the clinical differentiation of ET and PD and serve as a basis for the development of new strategies for the treatment of neurodegenerative diseases.

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