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Possible bradykinesia occurrence in lymphocyte division in Parkinson's disease

Yagmur INALKAC GEMICI [1,*], Irem TASCI [2], Muhammed DUNDAR [3], Nazmi OZGEN [3], Harika GOZDE GOZUKARA [3], Ahmet KOC [1]

[1]Department of Neurology, Faculty of Medicine, Celal Bayar University, Manisa, Türkiye
[2]Department of Neurology, Faculty of Medicine, Fırat University, Elazığ, Türkiye
[3]Department of Medical Biology and Genetics, Faculty of Medicine, İnönü University, Malatya, Türkiye
[4]Department of Biostatistics, Faculty of Medicine, İnönü University, Malatya, Türkiye

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Abstract

Lymphocytes have dopamine receptors, and low dopamine levels increase receptor synthesis. Lymphocytes may move slower in Parkinson's, which is characterized by low dopamine levels. We hypothesized that longer telomeres would indicate less lymphocyte division. We investigated whether leukocyte telomere length (LTL) is different in naïve Parkinson's disease (PD) patients and whether telomere length has clinical significance in determining telomere length in naïve Parkinson's patients. Naïve patients diagnosed with PD were included in this study. 29 naïve PD patients and 15 controls were included in the study. Subgroup analyses were performed according to MMSE and depression scores of PD patients. LTL was measured by RT-qPCR. Differences in LTL between the groups were examined. Clinical and demographic findings and LTL were examined and correlated using appropriate statistical methods. Forty-four participants meeting the inclusion criteria were included in the study. LTL was significantly longer in PD patients than in the control group ($p = 0.043$) and was positively correlated with clinical worsening of the disease. According to the Analysis of Moment Structures, evaluation total MMSE was 1.82, UPDRS was -1.53, and depression score was -.31 negatively correlated with telomere. LTL was found to be longer in naïve PD patients than in controls. Without other factors that could affect telomere; these findings support the hypothesis that leukocyte division could be slower in PD than the control group at the same age. Additional studies are needed on this subject. Additionally, a longer TL could be a marker for a better clinical course in PD.

Keywords: biomarkers, cognitive dysfunction, Parkinson's disease, telomer

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. The disease's main symptom is bradykinesia, which can include hypomimia, hypophonia, loss of associated movement during walking, and gastroparesis. Cognitive dysfunction, sleep disorders, and psychiatric and sensory symptoms are common non-motor symptoms in PD patients, along with motor symptoms (1).

Lymphocytes have dopamine receptors, and low dopamine levels increase receptor synthesis. Lymphocytes may move more slowly in Parkinson's, and longer telomeres may indicate less lymphocyte division. Telomeres, repetitive (TTAGGG) DNA sequences at chromosome ends, prevent chromosome ends from adhering and shortening each division (2). Telomeres shorten with each replication in somatic cells. Replicative senescence—permanent cell cycle arrest—occurs when telomere length is critically short (3). Functional telomeres are highly stable and protect chromosomes against degradation, recombination, or fusion; they lose 30–150 bases during cell division (4, 5). Shorter telomeres are associated with neurodegenerative diseases, cardiovascular diseases, diabetes, and cancer, but PD patients have longer, shorter, or unchanged telomeres (6, 7). In contrast, telomeres are shortened in numerous neurodegenerative diseases that are accompanied by cognitive changes, particularly Alzheimer's disease (8).

Parkinson's disease has been reported to develop secondary to the death of dopaminergic neurons in the brain. Additionally, it has also been reported PD severity is directly related to dopamine neuron loss in the substantia nigra pars compacta (SNc). Typically, the motor symptoms of PD appear only after 50–80% of the dopamine neurons are lost (1). In PD, the main pathological protein causing degeneration is alpha-synuclein (α-Syn), which forms Lewy bodies (1, 9). Lewy bodies play an important role in the pathophysiology of PD and other neurodegenerative diseases (10). Hence, researchers are

*Correspondence: yagmurgemici@outlook.com

focusing on early PD diagnosis and a marker that can diagnose the disease before cellular degeneration.

This study aimed to investigate TL in association with motor symptoms and systemic manifestations in patients with PD. Accordingly, we hypothesized that the leukocyte telomere length (TL) may indicate reduced leukocyte function. This study also examined whether PD patients' clinical and laboratory data correlate with telomere length.

2. Materials and methods

The study was designed as a cross-sectional, clinically controlled cohort study.

2.1. Study population

The study included 29 patients, aged 50–75, who were treated at the neurology outpatient clinic of our hospital between June 2020 and June 2021 and were diagnosed with PD based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria. To exclude the effects of drugs, all patients were newly diagnosed with PD and had not received treatment before the study. Patients with coronary artery disease, cancer, other neurodegenerative diseases, diabetes, or infections were excluded from the study. A control group of 15 healthy participants with similar demographic characteristics was included in this study.

On the MMSE, 23 is the optimal cutoff value for detecting cognitive dysfunction in the Turkish elderly population (11). Therefore, patients were divided into two groups based on their Mini-Mental State Examination (MMSE) scores: (i)≥24 (N = 15) and (ii) <24 (N = 14). All included individuals were educated. Additionally, the Unified Parkinson's Disease Rating Scale (UPDRS) was used to assess motor and non-motor symptoms of PD, the Geriatric Depression Scale (GDS) was used to assess depression, the Epworth Sleepiness Scale was used to evaluate daytime sleepiness, the Schwab and England Activities of Daily Living scale (SE-ADL) was used to evaluate daily life activities, and the Hoehn and Yahr (HY) scale was used to determine disease severity, all of which were administered by the same researcher. After administering these scales, approximately 5 mL of blood was obtained from the peripheral vein of each patient before the initiation of medication, and the specimens were stored at -20 °C until analysis. Hemograms and biochemical tests were routinely performed on patients with PD at their first admission.

2.2. DNA isolation

Genomic DNA was extracted directly from whole blood samples of patients and controls using the QIAamp DNA Blood Maxi Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Following elution of the purified DNA, they were quantified using a Denovix DS-11 FX+ spectrophotometer (A260/A280) (DeNovix, Wilmington, USA). DNA quality was evaluated by 1% agarose gel electrophoresis. After quantification, purified DNA samples were diluted to 20 ng/µL by nuclease-free water (Thermo Fisher Scientific, Waltham, MA, USA) and stored at -20 °C until the time of assay.

2.3. Real-time polymerase chain reaction

Real-time amplification of the telomere sequence was performed as described by Cawthon (12) with slight modifications. All samples were run on a StepOnePlus™ real-time polymerase chain reaction (PCR) system with the StepOne™ Plus v2.3 software (Applied Biosystems [AB] Foster City, CA, USA). A single-copy gene, 36B4, which encodes the acidic ribosomal phosphoprotein P0, was used as a control for the amplification of every sample. Each sample was analyzed in triplicate, and the averages were used for calculation after abnormal values were eliminated. Briefly, each 20-µL reaction was performed as follows: 150 ng DNA, 1 × SYBR Green master mix (RealQ Plus 2x Master Mix Green, Ampliqon, Odense, Denmark), 200 nM telomere forward primer (CGG TTT GTT TGG GTT TGG GTT TGG GTT TGG GTT TGG GTT), 200 nM telomere reverse primer (GGC TTG CCT TAC CCT TAC CCT TAC CCT TAC CCT TAC CCT). Except for the primers, the reaction mixture was the same for both telomeres and single-copy genes. For 36B4, 200 nM forward primers (CAG CAA GTG GGA AGG TGT AAT CC) and 200 nM reverse primers (CCC ATT CTA TCA TCA ACG GGT ACA A) were used. Negative control was used for contamination checks. Cycling conditions for telomere were 10 min at 95 °C followed by 30 cycles of 95 °C for 15 s and 55 °C for 2 min. For 36B4, they were as follows: 10 min at 95 °C followed by 30 cycles of 95 °C for 15 s and 59 °C for 1 min (13). Following amplification, StepOne™ Plus v2.3 software produced a C_T value for each reaction. Using these C_T values, we relatively compared the telomere content of each sample with the control group using the following procedure: First, the telomere/single-copy gene ratio was calculated by the formula $[2^{CT(telomeres)}/\ 2^{CT(36B4)}]^{-1} = 2^{-\Delta CT}$ for each sample, subsequently, the average $2^{-\Delta CT}$ value was calculated for the control group by dividing the total number of $2^{-\Delta CT}$ values of the control group by the number of individuals in the control group, and finally, the relative telomere content was determined as the telomere/single-copy gene ratio for each sample relative to the mean of the telomere/single-copy gene ratio for the control group using the following formula: $2^{-[\Delta CT(each\ sample)-\Delta CT(mean\ of\ the\ control)]} = 2^{-\Delta\Delta CT}$. The data obtained using this formula were analyzed for statistical significance ($p < 0.05$) among the three groups.

2.4. Statistical analysis

The sample size required to detect a significant difference according to telomere length was calculated to be at least 10 in each group (30 in total), considering a type I error (alpha) of 0.05, power (1-beta) of 0.8, and an effect size of 0.61.

Data were analyzed using IBM SPSS Statistics for Windows (version 22.0; Armonk, NY, USA). Qualitative data were compared using Pearson's chi-squared test. The normal distribution of the quantitative data was assessed using the Shapiro–Wilk test. Age and telomere lengths were normally distributed, summarized by mean ± standard deviation, and

compared by one-way analysis of variance. Tukey's post hoc test was used for pairwise comparisons. Non-normally distributed data were expressed as median, minimum, and maximum values. Two independent groups were compared using the Mann–Whitney U test. The effect of depression, UPDRS, and total MMSE on telomere length was determined with non-standardized and standardized Regression Weights using the AMOS program.

3. Results

In total, 189 patients diagnosed with PD visited our outpatient clinic during the study period. Of these, twenty-nine met the inclusion criteria and underwent a clinical evaluation. There was more than a year between the onset of motor symptoms and the first diagnosis, especially in patients with an MMSE score <24. Based on their complaints; these patients applied to different clinics for orthopedics, physical therapy, and rehabilitation before a diagnosis of PD was made. Therefore, the low MMSE scores of these patients did not exclude a diagnosis of PD. There was no difference in age and gender between the patient and control groups (p=0.102, p=0.500). Table 1 presents the clinical characteristics of the participants.

Table 1. Clinical data of the participants

Variable	PD patients		Control group		Test st.	p
	Median (sd)	Mean (min-max)	Median (sd)	Mean (min-max)		
Age	62.45 (5.99)	64 (50 - 75)	59.47 (52)	68 (61.43 – 5.73)	24473	0.102
MMSE	22.52 (5.8)	21 (10 - 30)	N/A	N/A		
UPDRS	35.97 (15.06)	35 (14 - 70)	N/A	N/A		
H&Y	1.81 (0.88)	1.5 (1 - 4)	N/A	N/A		
SE-ADL	0.75 (0.18)	0.8 (0.3 - 1)	N/A	N/A		
GDS	14.55 (6.56)	14 (3-26)	N/A	N/A		

UPDRS: Unified Parkinson's Disease rating scale, MMSE: minimental status examination, H&Y: Hoehn and Yahr, SE-ADL: Schwab and England Activities of Daily Living scale, GDS: Geriatric Depression Scale

*age was normally distributed and compared by one-way ANOVA

Telomere length was significantly longer in PD patients than in the control group (Table 2). Patients were divided into subgroups according to MMSE and depression scores. According to the subgroup analysis, the telomere length of the subgroups without cognitive dysfunction (MMSE≥24**)** and depression (DS<16) was significantly longer than the controls (p=0.013, p=0.039), while this significance disappeared in those with cognitive dysfunction or depression (p=0.840, p=0.928) (Table 3).

Fig. 1 presents the results of the full structural equation model analysis between TL and PD patients' clinics

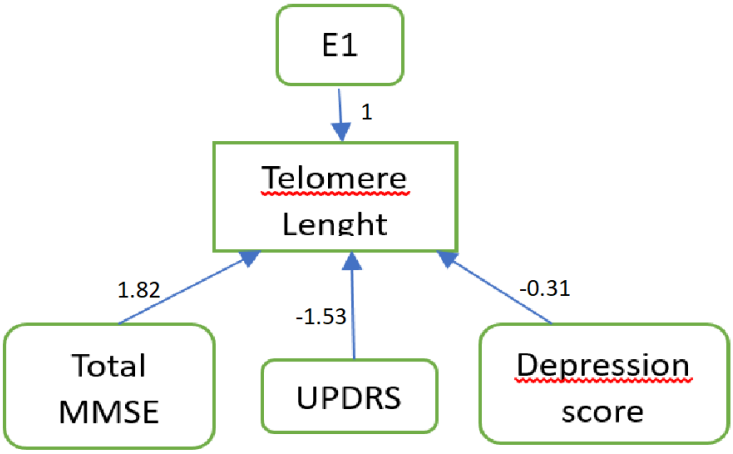

Fig. 1. Results of full structural equation model analysis

In the analysis of the correlation between TL and the severity of PD, we observed that shorter telomeres were positively correlated with worse clinical symptoms of the disease. The correlation of total MMT, UPDRS, and Depression Score with telomere length was evaluated with AMOS in our study. According to this evaluation, total MMSE was 1.82, UPDRS was -1.53, and depression score was -.31 negatively correlated with telomere.

Table 2. Telomere Length difference between patients and control group

Character	PD patients (N=29)	Control (N=15)	p
Age	62.4±5.9	59.4±4.7	0.102
TL	1.37±0.51	1.06±0.43	**0.043**

PD: Parkinson's Disease, TL: Telomere Length

Table 3. Telomere length differences in participants subgrouped by MMSE and depression

Groups	N	Mean±SD	Omnibus p	Pairwise p
MMSE				
Control	15	1.0632±0.4337	**0.012**	**Control – MMSE≥24: 0.013**
MMSE>24	14	1.5710±0.4670		MMSE≥24-MMSE<24: 0.058
MMSE<24	15	1.1609±0.4986		Control – MMSE<24: 0.840
Depression				
Control	15	1.06±0.43	**0.035**	**Control – DS<16: 0.039**
DS<16	20	1.47±0.52		DS>16 – DS<16: 0.192
DS>16	9	1.13±0.43		Control – DS>16: 0.928

MMSE: Minimental status examination, DS: Depression score

4. Discussion

This study found that TL was longer in naïve PD patients than in the control group, suggesting that leukocyte division may be reduced. Another important finding was that telomeres are shorter in PD patients with additional clinical worsening such as cognitive dysfunction and depression; This suggests that TL may also be important in-patient follow-up.

In a 2013 study, Schürks et al. followed up on patients at risk of PD for 13 years between 1997 and 2010. The authors used logistic regression to examine the relationship between TL and PD risk in peripheral blood samples. Interestingly, contrary to studies claiming that TL is lower or unrelated to PD, the authors showed that a longer TL increases the risk of PD (14). By contrast, Forero et al.'s meta-analysis found no correlation between PD and TL, suggesting that more studies should be conducted by using samples from different populations and intracranial areas (7). Wu et al. showed that TL was lower in Chinese patients with PD and noted that the presence of a leucine-rich repeat kinase 2 (LRRK2) mutation did not affect TL (15). In contrast, a recent genome-wide association study (GWAS) found no significant relationship between TL and PD. However, GWAS was conducted using clinical data from genome database patients, which prevented the exclusion of other factors affecting this relationship (16). In this study, we evaluated the association between PD and TL by excluding additional factors that could affect TL, including younger patients and age-matched controls. Similar to the findings of Schürks et al. (14), we found that TL was longer in patients than in controls. Although the reasons for longer TL in patients with PD remain unknown, several factors have been implicated. Neuroinflammation plays an important role in the pathogenesis of PD. It is known that toxic α-Syn oligomers trigger neuroinflammation by causing microglial activation. Moreover, neuroinflammation that occurs with neurodegeneration, albeit not as the initiating factor, causes an increase in telomerase activity (17). In similar studies, peripheral blood has been used in patients with PD (14, 15). Because intracranial samples cannot be used for ethical reasons, additional studies with simultaneous measurements of blood telomerase activity and telomere length are needed to evaluate this possibility. Measurement of peripheral TL could provide insights into the telomere status of patients. The second factor is a reduction in leukocyte division, which could be caused by the diminishing effect of dopamine on lymphocytes and the reduction in lymphocyte proliferation and differentiation (18, 19). Dopamine receptors in lymphocytes have been shown to increase dopamine receptor synthesis due to decreased dopamine levels (20). This phenomenon may explain the increased TL observed in patients with PD. In our study, blood samples were obtained from patients at the time of diagnosis, which is likely to increase the reliability of the data and also implies that leukocyte function and TL were not affected by the drugs. Considering the effect of dopamine on lymphocytes, we speculate that the longer TL in naïve PD patients may indicate that their bone marrow functions could be impaired. However, we did not determine bone marrow function in our patients, and new evidence is necessary to confirm that Parkinson's disease is associated with the bradymarrow. Since it would not be ethical to collect bone marrow from patients for this study, we thought that the telomere length of the cells produced from the bone marrow (peripheral cells) might reflect the bone marrow. However, this is an assumption, and further studies should be conducted to support this hypothesis. Jensen et al. recently showed that a low leukocyte count is a risk factor for PD (21). The mean leukocyte count of our patients was within the normal range.

In subgroup analysis, while the TL of MMSE≥**24 g**roup was significantly longer than that of the controls, the TL of MMSE<24 group was longer than that of the controls and shorter than that of **MMSE≥24 group**, although the difference was not statistically significant. This demonstrates that there may be additional factors that could cause a shorter TL. Cognitive dysfunction may be one such factor. Cognitive dysfunction is a common non-motor symptom of PD. Some studies have shown a relationship between cognitive dysfunction and short TL and a correlation between subcortical atrophy and short TL, while others have reported no such relationship (21-24). In the present study, due to contradictory results in the literature, we evaluated TL in patients with PD and cognitive dysfunction. In a recent study, Martin-Ruiz et al. evaluated patients with PD and found a correlation between the development of dementia and shortening. However, in that study, patients received treatment during the follow-up period (25). Another recent study evaluated the relationship between PD and TL and reported that the shortening increased the risk of dementia in patients with PD (26). Our findings support the

relationship between the severity of cognitive dysfunction and a shorter TL in patients who have cognitive impairment versus patients with cognitively normal PD; however, the difference was not statistically significant. Recent studies have stated that leukocyte telomere length is shorter in depression patients without comorbidities (26, 27). Mendes Silva et al. stated that the negative correlation between depression severity and TL suggests that it could be a potential biomarker (27). In our patients, telomeres were longer in PD patients without symptoms of depression than in controls, while this difference disappeared in those with depression, which is consistent with the literature. Additionally, a one-unit decrease in leukocyte telomere length was found to correlate with a 0.31-unit increase in depression score in PD patients. To our knowledge, there is no study in the literature evaluating the relationship between telomeres and depression in PD patients

In our study, the correlation between TL and the clinical scores of patients was investigated, and TL was positively correlated with MMSE scores and negatively correlated with UPDRS, and GDS scores. These findings suggest that a longer TL is associated with better clinical outcomes in patients with PD. Levstek et al. evaluated the TL effect on the symptomatology of PD and found that TL was associated with an increased risk of dementia in patients with PD (28). Martin-Ruiz et al. showed that telomere length was shortened more than in the control group in Parkinson's patients in 36 months and could be a marker that can be used to show clinical progression, especially in cognitive deterioration (25). However, additional studies are required to confirm this finding. Our findings support and add to the literature by showing that telomere length worsens cognitive, psychiatric, and motor function in naïve PD patients.

Our study has several limitations. First, it included a small number of patients. Nevertheless, it could be asserted that the number of patients was sufficiently high due to the creation of a homogeneous group of unmedicated patients who met the inclusion and exclusion criteria. Another important limitation is the low sensitivity of TL as a biomarker because it is affected by numerous conditions, such as aging, neurodegenerative diseases, and cancer.

A longer TL may suggest that the leukocytes generated from the bone marrow and involved in the innate immune response in early-stage PD form remarkably slowly or divide slowly. This suggests that bone marrow may be biomarker of early-stage PD. However, because TL alone cannot show this, studies with additional data are required to evaluate patients with early-stage PD. On the other hand, our results indicate that a longer TL is associated with a better clinical course of PD, which suggests that TL could be an essential parameter in the follow-up and evaluation of prognosis in patients with PD. There is an obvious relationship between shorter telomere length and worse clinical conditions especially depression and cognitive dysfunction in patients with PD. Additional studies involving larger groups are needed to determine this relationship more clearly.

Ethical Statement

Ethical approval was obtained from the Malatya Clinical Research Ethics Committee (Decision date: 05.02.2020, decision no: 2020-05). Written consent was obtained from all patients.

Conflict of interest

Conflict of interest was absent.

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None to declare.

Authors' contributions
Concept: Y.I.G, A.K., Design: Y.I.G, A.K., Data Collection or Processing: Y.I.G, I.T., M.D., N.O., Analysis or Interpretation: Y.I.G., I.T., H.G.G., Literature Search: Y.I.G, I.T., M.D., N.O., H.G.G., A.K., Writing: Y.I.G, I.T., M.D., N.O., H.G.G., A.K.

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