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The effect of serum homocysteine, vitamin B12, and folate levels on cognition in Parkinson's disease and Parkinson's disease dementia

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Abstract

Homocysteine is an amino acid formed during methionine metabolism that contributes to neurodegeneration by inducing an excitotoxic response. This study aimed to investigate the relationship between cognitive impairment and serum homocysteine, vitamin B12 and folate levels in Parkinson's disease (PD). A total of 64 patients, 46 with PD and 18 with Parkinson's Disease Dementia (PDD), who were followed up in the Movement Disorders Outpatient Clinic, were included in the study. To assess cognitive performance, both patient groups underwent the Standardized Mini-Mental State Examination (MMSE) and a clock drawing test. The correlations between serum vitamin B12, homocysteine and folate levels, and cognitive test scores were evaluated for both patient groups. In the PD group, higher levels of vitamin B12 and folate, as well as lower homocysteine levels, were found compared to the dementia group, with statistical significance observed only for vitamin B12 levels. In terms of the MMSE total scores, as well as its subcategories; in the registration, recall, and attention sections, PD patients were found to perform better than the dementia group. A negative correlation of 32.2% was found between MMSE total scores and homocysteine levels, while a positive correlation of 54.2% was observed between folate levels and attention. A positive correlation was found between the total MMSE scores and clock drawing test scores in both patient groups, but no significant relationship was found between clock drawing test scores and serum vitamin levels, or homocysteine levels. In PD, a negative correlation was observed between homocysteine levels and total MMSE scores, while a positive correlation was found between folate levels and attention in PDD.

Keywords: Parkinson's disease, homocysteine, folate, vitamin B12, cognition, Parkinson's dementia

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease in which motor symptoms are prominent, but non-motor symptoms are also observed [1,2]. Motor symptoms include bradykinesia, resting tremor, and rigidity, while non-motor symptoms may include anosmia, mood disturbances, excessive salivation, constipation, and REM sleep behavior disorder [3]. Considering mortality and morbidity, cognitive decline is considered one of the important non-motor symptoms [4]. Cognitive impairment in PD is six times more than in the healthy population. Cognitive decline may present as subjective cognitive impairment, mild cognitive impairment, or dementia [5]. Mild cognitive impairment have been observed in 36% of newly diagnosed PD patients, and it has been determined that almost half of the patients may progress to Parkinson's disease dementia (PDD) within the first 10 years [6,7].

Parkinson's disease mild cognitive impairment (PD-MCI) is a cognitive disorder seen in the early stages of disease, with memory and visuospatial functions most commonly affected. In PDD, attention, visuospatial, and executive functions are typically significantly impaired early on, while language functions are relatively preserved, with moderate impairments in episodic memory [4]. Depressive symptoms and visual hallucinations have been found to be more common than in Alzheimer's disease [8]. Older age, severe motor symptoms and bradykinesia, speech disorders, depression, older age at PD diagnosis, higher Hoehn and Yahr stages, lower education level, and male gender are risk factors for the development of dementia [6].

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Regarding cognitive decline development, homocysteine, considered a normal metabolic product, has been shown to cause neuronal damage at high concentrations, increase dopaminergic degeneration, and serving as a risk factor for the development of cognitive decline in PD [9,10]. Homocysteine exerts an agonistic effect on the N-methyl-D-aspartate (NMDA) receptor, activating the receptor and inducing an excitotoxic response [11]. Elevated homocysteine levels may be due to vitamin B12, B6, folate or betaine deficiencies. Levodopa is known to play a role in folic acid metabolism and has a dose-response relationship with homocysteine [12].

This cross-sectional study compared blood levels of homocysteine, vitamin B12, and folate with cognitive test scores—including total and subdomain Mini-Mental State Examination (MMSE) scores and the clock drawing test—in patients with Parkinson's disease and Parkinson's disease dementia. It also aimed to examine the association between these nutritional markers and overall cognitive status.

Material and Methods

Patient Selection

In this cross-sectional and retrospective study, the files of Parkinson's disease patients followed up at the Movement Disorders Clinic of Haydarpaşa Numune Training and Research Hospital were reviewed. Patients who had undergone serum vitamin B12, folate, and homocysteine level measurements within a 3-month period before or after their Standardized MMSE and clock drawing test were included in the study. Patients with conditions that could affect homocysteine levels, such as diabetes, chronic kidney failure, hypothyroidism, malignancy, and those who had not fasted in the morning, as well as patients with Parkinson's Plus Syndrome or suspected of having it, were excluded from the study.

Processing of Blood Samples

The serum levels of homocysteine, folate, and vitamin B12 of the patients were measured using the Abbott Architect i2000sr Immunoassay Analyzer with chemiluminescent immunoassay method.

Cognitive Assessment

The patients underwent the MMSE and the clock drawing test. The clock drawing test was scored out of 4 points. A circle/square/rectangle drawn closed (the outer frame of the clock) was given 1 point, having the numbers in the correct place and position was awarded 1 point, all 12 numbers present (complete) scored 1 point, and the correct positioning of the hour and minute hands (11:10) was given 1 point [13].

Statistical Analysis

Statistical analyses were performed using SPSS version 29. Normality tests were conducted using the Shapiro-Wilk test, histograms, and Q-Q plots. For pairwise comparisons, when the data followed a normal distribution, the independent t-test was used, and when the distribution was not normal, the Mann-Whitney U test was applied. In correlation analyses, when the data were normally distributed, Pearson's correlation test was used, and when they were not normally distributed, Spearman's correlation test was applied. A p-value of <0.05 was considered statistically significant.

Ethical Approval

This study was approved by the Ethics Committee of Haydarpaşa Numune Research and Training Hospital (Date: 25.04.2016 Number: 2016/52)

Results

The records of 246 patients who were regularly followed up between 2014 and 2016 were retrospectively reviewed for the study. Patients who had undergone the SMME and the clock drawing test, with test dates and blood measurements of vitamin B12, folate, and homocysteine taken within a 3-month period before or after the tests, were included in the study. After applying the exclusion criteria, 46 PD patients and 18 PDD patients were included for further analysis.

Of the 46 PD patients, 30 were male. Among the 18 PDD patients, 13 were male. The mean age of the PD group was 67.59±12.29 years, and the mean age of the PDD group was 76.33±4.98 years.

In the Parkinson's group, higher levels of vitamins, as well as lower homocysteine levels, were observed compared to the dementia group. However, statistical significance was only observed in the vitamin B12 levels (p=0.040) (Table 1).

Table 1. Comparison of serum homocysteine, vitamin b12, and folate levels between patient groups

	PD	PDD	p-value
Homocysteine (µmol/L)	17.83±8.38	18.91±6.77	0.389
Vitamin B12 (pg/ml)	272.87±83	246.67±68.83	0.040
Folate (ng/ml)	5.27±2.17	4.89±1.72	0.246

PD: Parkinson's disease, PDD: Parkinson's disease dementia

When examining the performance on the MMSE, it was found that the performance of the PD patients was significantly better than that of the PDD group (p=0.005). PD patients were found to be more successful in the registration, recall, and attention sections compared to the dementia group (p=0.030, p<0.001, p=0.030, respectively) in MMSE.

When comparing the MMSE scores with laboratory values, a negative correlation of 32.2% was found between the MMSE total score and homocysteine levels in the Parkinson's group, meaning that as serum homocysteine levels increased, cognitive decline became more prominent. However, no such correlation was observed in the subcategory scores (Figure 1). A Pearson correlation analysis between serum vitamins levels, and the MMSE total and subcategory scores revealed no significant relationship.

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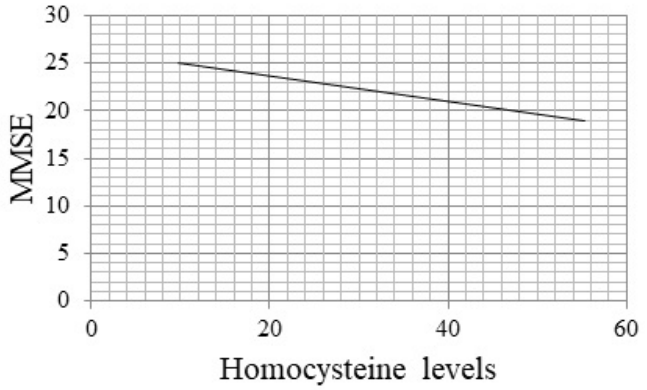

Figure 1. The relationship between MMSE score and serum homocysteine levels in Parkinson's disease patients

In the PDD group, no relationship was found between MMSE total score and measured serum values. However, a positive correlation of 54.2% was found between folate levels and attention in the subcategory scores.

A Spearman correlation analysis between the MMSE total scores and clock-drawing test scores revealed a positive correlation in both patient groups, with correlation percentages of 76.8% in the PD group and 87.5% in the PDD group. In the subcategory scores, positive correlations were found between clock drawing and orientation, attention, recall, and language in both groups (Table 2). Additionally, as observed in the MMSE scores, PD patients performed better on the clock-drawing test compared to the PDD group ($p<0.001$).

Table 2. Correlation between clock drawing test and MMSE total and subcategory scores in the groups

		MMSE	Orientation	Registration	Attention	Recall	Language
		PD group					
Clock drawing	**Corr. coeff.**	0.768*	0.558*	0.147	0.704*	0.438*	0.520*
	Sig. (2-tailed)	<0.001	<0.001	0.329	<0.001	0.002	<0.001
		PDD group					
Clock drawing	**Corr. coeff.**	0.875*	0.806*	0.335	0.705*	0.714*	0.778*
	Sig. (2-tailed)	<0.001	<0.001	0.174	0.001	<0.001	<0.001

MMSE: Mini-Mental State Examination, PD: Parkinson's disease, PDD: Parkinson's disease dementia

No significant relationship was found between the clock-drawing test scores and serum values measured in both patient group.

Regarding levodopa use, 37 Parkinson's patients (80.4%) were using levodopa, while 9 (19.6%) were not. All patients in the dementia group were using levodopa. In the PD group, the mean duration of levodopa use was 4.37 years, with an average levodopa dose of 372.97 mg/day (min 200-max 700). In the PDD group, the mean duration of levodopa use was 5.22 years, with an average levodopa dose of 411.11 mg/day (min 300-max 700).

Although the average B12 and folate levels of 37 patients using levodopa were found to be higher than those not using it, serum homocysteine levels were also found to be higher. The average B12 value of patients using levodopa was 279.81±83.79, folate value was 5.41±2.20 and homocysteine value was 18.59±9.03. In patients not using it, these values were determined as 244.33±82.35, 4.65±2.07 and 14.7±3.76, respectively. The differences between the values examined did not show statistical significance (Table 3). Since all 18 patients in the PDD group used levodopa, these data could not be analyzed in this group.

Table 3. Serum vitamin B12, folate, and homocysteine levels in Parkinson's disease patients using and not using levodopa

	Levodopa use	Number	Mean	St. dev.	p-value
Homocysteine (µmol/L)	No	9	14.7	3.76	0.054
	Yes	37	18.59	9.03	
Folate (ng/ml)	No	9	4.65	2.07	0.349
	Yes	37	5.41	2.20	
Vitamin B12 (pg/ml)	No	9	244.33	82.35	0.270
	Yes	37	279.81	83.79	

St. dev.: standart deviation

Discussion

In this study, the effects of homocysteine and its metabolites vitamin B12 and folate levels, which have effects on neurodegeneration, on cognition in Parkinson's patients were investigated. A negative correlation was observed between homocysteine levels and SMMT total scores in Parkinson's patients, and a positive correlation was observed between folate levels and attention in PD patients. A positive correlation was

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found between the clock drawing test and SMMT total scores and orientation, attention, recall and language subheadings in all patients, but no significant relationship was found between the laboratory values examined.

Cognitive decline is a common non-motor finding. Both α-synuclein and amyloid protein dysmetabolism, as well as cholinergic deficiencies, make a contribution to cognitive decline in PD [14]. A study that followed patients diagnosed with PD for cognitive decline and MCI for an average of 5 years found that 28% of patients were diagnosed with dementia by the sixth year [15].

Male gender, Alzheimer's pathology, sleep and mood disorders, cardiovascular risk factors, low uric acid levels, smoking, pesticide exposure, and family history are known risk factors for the development of dementia [16]. Structural changes such as basal choroid plexus volume and white matter lesions have also been closely related with cognitive decline in PD patients [17,18].

Several studies have highlighted the effects of nutrition. A 10-week Mediterranean diet intervention in PD patients showed significant improvements in executive function, language, attention, concentration, working memory, and total scores in the MoCA test, while no changes were observed in the control group. This improvement was attributed to the cardiovascular risk reduction and antioxidant-rich diet, including vitamin E, C, and folate [19]. Cross-sectional and observational studies have also shown that ketogenic diets and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets are associated with reduced cognitive decline [20].

Elevated plasma homocysteine has been identified as a risk factor for neurodegenerative diseases, being higher in Parkinson's patients compared to healthy controls and correlated with disease progression [21]. Patients with hyperhomocysteinemia have been found to have worse cognitive performance and higher depression levels, as seen in our patient group [22]. Another study on early-stage Parkinson's disease patients supports these findings, showing that higher homocysteine levels predicted greater cognitive decline, while low vitamin B12 levels predicted worse mobility [23]. PD patients with low vitamin B12 levels were found to have higher Hoehn-Yahr stages, worse cognitive performance, and neuropathy was more common in these patients [24]. A study comparing PD patients with and without dementia found that patients with dementia had lower folate and higher homocysteine levels, suggesting that these markers could be useful for diagnosing cognitive impairments in Parkinson's patients [25]. Additionally, low B12 and folate levels and high homocysteine concentrations have been shown to be independently associated with Parkinson's disease dementia compared to non-dementia PD patients [26].

Levodopa use has been associated with lower B12 and folate levels in Parkinson's patients, which in turn is linked to cognitive decline. In our patient group, lower homocysteine levels were observed in a small number of patients who did not use levodopa (9), while B12 and folate levels were higher in those who did use it, but homocysteine levels were higher. Although our study suggests that levodopa has an effect on homocysteine, the differences detected were not statistically significant because it was a small sample group [27].

Limitations

The study has many limitations. The design of our study was retrospective and cross-sectional. Although replacement therapy was given to appropriate patients, it could not be evaluated whether long-term cognitive follow-up and improvement in cognitive function would occur after increasing low vitamin B12 and folate levels.

Since homocysteine levels are affected by many diseases and conditions, the study exclusion criteria caused too much elimination in the patient population and the study was conducted with a small patient group and does not reflect the general population.

Since the study was planned retrospectively, patients were only globally assessed for depression and sleep quality in the first section of the UPDRS. Since most patients did not have a geriatric depression scale and Pittsburgh Sleep Quality Index in a time window suitable for the serum values examined, the results of the few patients present were not included in the study because they would not be statistically significant.

Neuropsychological test battery (NTB) was applied to the patients due to cognitive retardation, but in most of the files there was no time relationship between the laboratory results examined with NBT. Since the educational status was also diverse, MOCA test was applied to some patients. In order to equalize the data, only MMSE and clock drawing test could be used for cognitive data. This situation provided only a superficial view of cognitive impairment and limited the detailed examination of the patients.

Conclusion

Our study found that serum homocysteine levels had a negative impact on MMSE scores in PD patients, while serum folate levels were positively correlated with attention in PDD patients. The clock-drawing test scores were positively correlated with MMSE total scores and subcategories such as orientation, attention, recall, and language, but no significant relationship was found with laboratory values. Further studies with a larger patient population and more detailed neuropsychological assessments are needed to understand the effect of nutrition.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical Approval
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References

1. Zesiewicz TA. Parkinson disease. Continuum (Minneap Minn). 2019;25:896-918.
2. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. Nat Rev Dis Primers. 2017;3:17013.
3. Zafar S, Yaddanapudi SS. Parkinson Disease. [Updated 2023 Aug 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
4. Hanagasi HA, Tufekcioglu Z, Emre M. Dementia in Parkinson's disease. J Neurol Sci. 2017;374:26-31.
5. Aarsland D, Creese B, Politis M, et al. Cognitive decline in Parkinson disease. Nat Rev Neurol. 2017;13:217-31.
6. Marinus J, Zhu K, Marras C, et al. Risk factors for non-motor symptoms in Parkinson's disease. Lancet Neurol. 2018;17:559-68.
7. Williams-Gray CH, Mason SL, Evans JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry. 2013;84:1258-64.
8. Emre M. Dementia associated with Parkinson's disease. Lancet Neurol. 2003;2:229-37.
9. Mischley LK. Nutrition and nonmotor symptoms of Parkinson's disease. Int Rev Neurobiol. 2017;134:1143-61.
10. Ueland PM. Homocysteine species as components of plasma redox thiol status. Clin Chem. 1995;41:340-2.
11. Lipton SA, Kim W-K, Choi Y-B, et al. Neurotoxicity associated with dual actions of homocysteine at the N-methyl-D-aspartate receptor. Proc Natl Acad Sci U S A. 1997;94:5923-8.
12. Paul R, Borah A. L-DOPA-induced hyperhomocysteinemia in Parkinson's disease: Elephant in the room. Biochim Biophys Acta. 2016;1860:1989-97.
13. Cangöz B, Karakoç E, Seleker K. The norm determination and validity-reliability studies of clock drawing test on Turkish adults and elderlys (ages 50 and over). Turkish Journal of Geriatrics. 2006;9:136-42.
14. Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. Lancet Neurol. 2012;11:697-707.
15. Pigott K, Rick J, Xie S X, et al. Longitudinal study of normal cognition in Parkinson disease. Neurology. 2015;85:1276-82.
16. Gonzalez-Latapi P, Bayram E, Litvan I, Marras C. Cognitive impairment in Parkinson's disease: epidemiology, clinical profile, protective and risk factors. Behav Sci (Basel). 2021;11:74.
17. Lee S-J, Kim J-S, Yoo J-Y, et al. Influence of white matter hyperintensities on the cognition of patients with Parkinson disease. Alzheimer Dis Assoc Disord. 2010;24:227-33.
18. Jeong S H, Jeong H J, Sunwoo M K, et al. Association between choroid plexus volume and cognition in Parkinson disease. Eur J Neurol. 2023;30:3114-23.
19. Paknahad Z, Sheklabadi E, Derakhshan Y, et al. The effect of the Mediterranean diet on cognitive function in patients with Parkinson's disease: a randomized clinical controlled trial. Complement Ther Med. 2020;50:102366.
20. Knight E, Geetha T, Burnett D, Babu JR. The role of diet and dietary patterns in Parkinson's disease. Nutrients. 2022;14:4472.
21. Fan X, Zhang L, Li H, et al. Role of homocysteine in the development and progression of Parkinson's disease. Ann Clin Transl Neurol. 2020;7:2332-8.
22. O'Suilleabhain PE, Sung V, Hernandez C, et al. Elevated plasma homocysteine level in patients with Parkinson disease: motor, affective, and cognitive associations. Arch Neurol. 2004;61:865-8.
23. Christine CW, Auinger P, Joslin A, et al. Vitamin B12 and homocysteine levels predict different outcomes in early Parkinson's disease. Mov Disord. 2018;33:762-70.
24. McCarter SJ, Teigen L M, McCarter AR, et al. Low vitamin B12 and Parkinson disease: potential link to reduced cholinergic transmission and severity of disease. Mayo Clin Proc. 2019;94:757-62.
25. Liu X, Dong T, Zhang Y, et al. Relationship between serum homocysteine level and cognitive impairment in patients with Parkinson‘s disease. Pteridines. 2019;30:177-82.
26. Sławek J, Roszmann A, Robowski P, et al. The impact of MRI white matter hyperintensities on dementia in Parkinson's disease in relation to the homocysteine level and other vascular risk factors. Neurodegener Dis. 2013;12:1-12.
27. Triantafyllou NI, Nikolaou C, Boufidou F, et al. Folate and vitamin B12 levels in levodopa-treated Parkinson's disease patients: their relationship to clinical manifestations, mood and cognition. Parkinsonism Relat Disord. 2008;14:321-5.