ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Effect of Homocysteine Levels on Cognitive and Motor Performance in Patients with Parkinson's Disease

Parkinson Hastalarında Homosistein Düzeyinin Kognitif ve Motor Performans Üzerine Etkisi

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ABSTRACT Objective: As well as being a risk factor for vascular diseases, hyperhomocysteinemia is also a risk factor for neurodegeneration. The present study examines the effect of hyperhomocysteinemia on cognitive and motor performance in patients with Parkinson's disease (PD). **Material and Methods:** 46 PD patients monitored by us and 30 volunteers without a cronic disease to cause hyperhomocysteinemia compatible with this population were included in the study. Blood levels of folate, vitamin B12 and homocysteine of both groups were measured and compared. In the patient group, Standardized Mini Mental Test (SMMT) and The Unified Parkinson's Disease Rating Scale (UPDRS) scores were determined and serum homocysteine levels were measured to see if there was a correlation between these two. Furthermore, the effect of levodopa intake on blood vitamin B12, folate and homocysteine levels in patients was examined. The assumed significance level is $p < 0.05$. **Results:** Vitamin B12 and folate levels were significantly lower in the patient group than in the control group, whereas homocysteine levels were significantly higher in the patient group. Levodopa intake had no significant effect on the examined levels. Elevated homocysteine levels resulted in lower SMMT scores and higher UPDRS scores. **Conclusion:** Many other studies have found hyperhomocysteinemia in PD patients and indicated that hyperhomocysteinemia was one of the causes of decreased cognitive and motor performance during the course of disease. With its finding of decreased performance in the patients, the present study also supports the above mentioned studies and recommends B12 and folate supplements in order to slow down the disease progression.

Keywords: Parkinson's disease; hyperhomocysteinemia; vitamin B12; cognition; motor performance

ÖZET Amaç: Hiperhomosisteinemi vasküler hastalıkların yanısıra nörodejenerasyon için de risk faktörüdür. Bu çalışmada Parkinson hastalarında hiperhomosisteineminin kognitif ve motor performans üzerine etkisi incelenmiştir. **Gereç ve Yöntemler:** Çalışmaya tarafımızca takip edilen ve hiperhomosisteinemiye sebep olacak bir kronik hastalığı olmayan 46 Parkinson hastası ve bu popülasyona uygun 30 gönüllü birey alınmıştır. Her iki grubun kan folat, vitamin B12 ve homosistein düzeyleri ölçülerek karşılaştırılmıştır. Hasta grubunda Standardize Mini Mental Test (SMMT) ve The Unified Parkinson's Disease Rating Scale (UPDRS) skorları ile serum homosistein düzeyi arasında korelasyon olup olmadığı bakılmıştır. Ayrıca hastalarda levodopa kullanımının kan vitamin B12, folat ve homosistein düzeyine etkisi incelenmiştir. İstatistiksel olarak $p<0,05$ anlamlı kabul edilmiştir. **Bulgular:** Parkinson hastalarının oluşturduğu grupta kontrol grubuna kıyasla vitamin B12 ve folat düzeyleri anlamı düşük, homosistein düzeyleri ise anlamlı derecede yüksek saptandı. Levodopa kullanımının bakılan değerlere anlamlı etkisi saptanmadı. Homosistein düzeyi arttıkça SMMT skoru düşüyor, UPDRS skoru yükseliyordu. **Sonuç:** Pek çok çalışmada Parkinson hastalarında hiperhomosisteinemi saptanmış ve hiperhomosisteineminin hastalık sürecinde kognitif ve motor performans düşüklüğünün bir nedeni olarak gösterilmiştir. Biz de bu çalışmaları destekler nitelikte hastalarımızın daha düşük performans sergilediğini göstermekte ve hastalık progresyonunu yavaşlatmak amacı ile B12 ve folat desteği verilmesini önermekteyiz.

Anahtar Kelimeler: Parkinson hastalığı; hiperhomosisteinemi; B12 vitamini; kognisyon; motor performans

Homocysteine is a sulfur-containing amino acid biosynthesized during methionine metabolism.[1] While plasma homocysteine level is yet to be standardized, the normal level is usually 5 to 15 μmol/L in the blood sample collected after 12 hours of fasting.[2] Homocysteine acts as an agonist at the glutamate binding site of the N-metil-D-aspartat (NMDA) receptor and causes excitotoxic response by activating this receptor.[3] Elevated homocysteine levels, thus, is a potential cause for neurodegenerative effects. Vitamin deficiencies, old age, male sex, post menopause, chronic renal disease, hypothyroidism, some drugs such as methotrexate, nicotinic acid and genetic factors are causes for hyperhomocysteinemia.[4] Hyperhomocysteinemia is a risk factor for vascular diseases, Alzheimer's disease, dementia, and cortical and hippocampal atrophy.[5-7] Recent studies have found elevated homocysteine levels in Parkinson disease (PD) patients as well, and showed that levodopa intake results in elevated homocysteine levels.[8] Additionally, animal experimentations found that levodopa and dopamine decarboxylase administration resulted in increased conversion of S-adenosylmethionine into S-adenosylhomocysteine and homocysteine catalyzed by catechol-O-methyltransferase, and therefore, in a twofold increase in homocysteine concentrations.[9]

Besides causing disorders in vascular structures, elevated homocysteine levels have neurotoxic effects. Reduced plasma and cerebrospinal fluid (CFS) levels of folate and vitamin B12 and elevated homocysteine levels are detected in patients with memory dysfunction. Previous studies have shown lower motor performance, depression, and higher cognitive decline in Parkinson's disease patients with elevated homocysteine levels.[10]

Our study aims to show the role of the metabolites vitamin B12 and folate in neurodegenerative processes by measuring the homocysteine levels and the levels of vitamin B12 and folate involved in its metabolism in patient and control groups. The study also examines the effect of levodopa intake, which is regarded as a cause of hyperhomocysteinemia, on the homocysteine levels in our patient group.

MATERIAL AND METHODS

46 PD patients, who have been monitored by our Movement Disorders Clinic in Haydarpaşa Training Hospital and had no metabolic diseases that could cause hyperhomocysteinemia like chronic renal diseases, hypothyroidism as well as 30 volunteers compatible with this patient population, were included in the study. There was a gender difference between two groups, but age means were equal. Because old age, male sex and post menopause were risk factors for hyperhomocysteinemia, participants were chosen by age mostly. Blood levels of folate, vitamin B12 and homocysteine of both groups were measured and compared. In order to evaluate the cognitive performance, Standardized Mini Mental Test (SMMT) was administered in the patient group and the correlation between serum homocysteine levels and SMMT scores was examined. In the patient group, The Unified Parkinson's Disease Rating Scale (UPDRS) scores were determined and serum homocysteine levels were measured to see if there was a correlation between these two. Furthermore, the effect of levodopa intake on blood vitamin B12, folate and homocysteine levels in patients was examined.

IBM SPSS Statistics 22 software was used for data analysis. Besides determinant statistics, One Sample T-Test was used for patient and control group comparisons and Independent Samples T-Test was used in patient group. Pearson correlation coefficient was used as a measure of correlation. The assumed significance level is $p < 0.05$.

Ethics committee approval was obtained for this study.

Informed consent was obtained from the participants included in the study.

RESULTS

Table 1 shows the age, sex and examined biochemical values of the study groups. Comparison between patient and control groups revealed

significantly lower vitamin B12 and folate levels in the patient group than in the control group, whereas homocysteine levels were found to be significantly higher in the patient group ($p<0.05$).

In the patient group, 37 (80.4%) patients were taking levodopa while 9 (19.6%) were not taking it. Serum homocysteine, vitamin B12 and folate levels of the patients taking levodopa were higher than those who were not taking it; however, there was no significant difference (Table 2).

The average of SMMT scores of the patient group was 23,9. Comparison between the SMMT scores and laboratory values of the patient group revealed a 32.2% inverse relationship between SMMT scores and homocysteine levels, which means as the homocysteine levels increased cognitive decline became more pronounced (Figure 1).

The UPDRS scores of the patient group's mean was 31,5. When compared, the UPDRS scores and homocysteine levels were found to have a 38.2% direct relation, which means elevated homocysteine levels resulted in increased UPDRS scores (Figure 2).

DISCUSSION

Parkinson's disease is a progressive chronic disorder developing predominantly with loss of dopaminergic neurons in extrapyramidal system and impairing the individual's functional capacity with a large number of motor and non-motor features such as tremor at rest, rigidity, bradykinesia, and postural instability.[11] There are many previous publications studying the factors held responsible for neurotoxicity and playing a role in pathogenesis among which is a cross-sectional study carried out approximately 20 years ago which was the first study to find an increase in homocysteine levels in PD patients compared to the control group.[12] Supporting this 20-year-old study, our study also found higher homocysteine levels in PD patients than in control group. Furthermore, vitamin B12 and folate levels were found to be significantly lower in the patient group. *In vivo* studies on PD models aiming to reveal neurotoxicity showed that the number of dopaminergic neurons killed by the specific dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was greater in rats with elevated serum homocysteine levels and two bioflavonoids called fisetin and hesperidin treatment reduced homocysteine levels.[13,14] *In vitro* studies, however, showed direct toxic effects of homocysteine on cortical neurons, postnatal cerebellar granule neurons, cerebellar Purkinje cells, dorsal root ganglion neurons, and trigeminal sensory neurons.[15]

TABLE 1: Demographics and biochemical levels of the groups.

		Sex				
	Age (year)	Female	Male	Vitamin B12 (pg/ml)	Folate (ng/ml)	Homocysteine (µmol/L)
Patients with Parkinson's Disease	67,5±12,2	16	30	272,8 (117-502)	5,2 (2,1-10,9)	17,8 (9,8-55,2)
Control Group	69,6±9,2	21	9	361,7 (120-1336)	7,5 (3,8-18,9)	13,3 (8,3-21,7)

TABLE 2: Vitamin B12, folate and homocysteine levels in patients taking and not taking levodopa.

	Levodopa Intake	Number of Patients	Average	Standard Deviation	p
Homocysteine (µmol/L)	No	9	14.7	3.76019	0.054
	Yes	37	18.5	9.02790	
Folate (ng/ml)	No	9	4.6	2.07190	0.349
	Yes	37	5.4	2.19610	
Vitamin B12 (pg/ml)	No	9	244.3	82.34986	0.270
	Yes	37	279.8	83.78936	

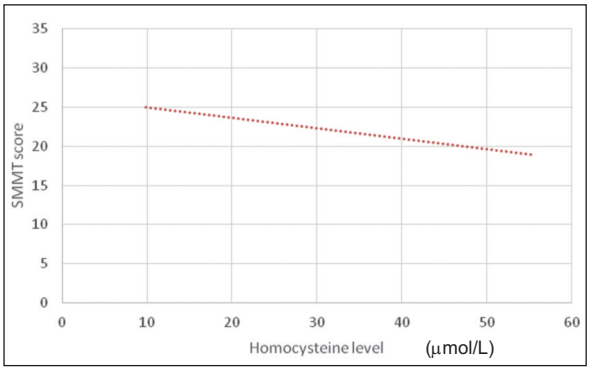

FIGURE 1: Comparison between SMMT scores and homocysteine levels.

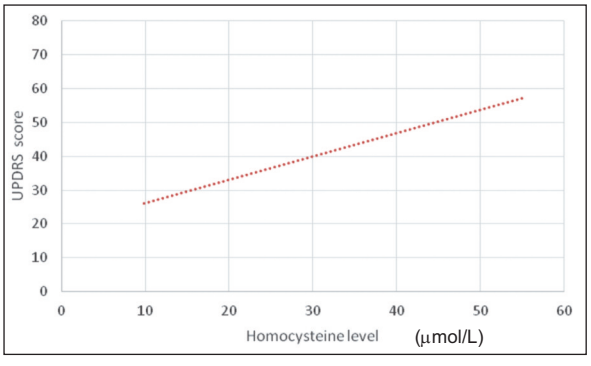

FIGURE 2: Comparison between UPDRS scores and homocysteine levels.

A positive correlation was found between homocysteine levels and UPDRS scores in patients with hyperhomocysteinemia.[16] In the meta-analysis involving 15 study; PD patients with cognitive disfunctions had higher homocysteine levels and lower vitamin B12 and folate levels.[17] Another study by Prins et al. revealed that elevated serum homocysteine levels in PD patients caused worse mood, and impaired motor and cognitive function compared to control group.[10] In a 2-year follow-up study of early PD patients; low vitamin B12 at baseline predicted greater worsening of mobility however elevated homocysteine levels predicted greater cognitive decline.[18] Especially, homocysteine was inversely correlated with tests of memory and verbal fluency in Parkinson disease.[19] Similarly, our study found a negative correlation between elevated serum homocysteine levels and SMMT scores, and showed that an increase in homocysteine levels resulted in a decrease in cognitive performance. Just like in SMMT scores, elevated homocysteine levels resulted in reduced performance in UPDRS scores which measure predominantly the motor performance.

Levodopa is O-methylated by catechol-O-methyltransferase (COMT) in brain and peripheral tissues which requires Sam as the methyl donor and SAM is converted into dimethylated S-adenosyl-homocysteine (SAH). Subsequently, SAH is quickly converted into homocysteine. Homocysteine is also obtained from dietary methionine and this process requires vitamin B12 and folate as cofactors.[9,20] Long-term levodopa intake also increases COMT activity. In chronic levodopa intake, levodopa activity and levels are reduced based on accumulation of levodopa metabolites and the increase in COMT activity. As a result, levodopa tolerance is developed and more levodopa is needed. Therefore, level of homocysteine, a breakdown product of levodopa, is also increased. A study by Nissinen et al. showed that low doses of levodopa did not affect homocysteine levels while chronic use of high doses of levodopa affected homocysteine levels remarkably. This increase in plasma homocysteine levels was thought to be due to levodopa therapy rather than PD pathogenesis.[8] Paul and Borah asserted that levodopa induced hyperhomocysteinemia could responsible for levodopa induced dyskinesia.[21] Miller et al. reported reduced vitamin B12 and folate levels in patients taking levodopa as a result of this cycle.[22] Another study found a negative correlation between homocysteine levels and vitamin B12 and folate levels, and suggested that homocysteine levels would be reduced with vitamin B12 and folate supplements in patients taking levodopa. Accordingly, it was thought that disease progression could be slowed down by giving vitamin B12 and folate supplements to patients with hyperhomocysteinemia.[15,23] Our study, however, did not find such a difference in the patient group between patients taking and not taking levodopa.

CONCLUSION

In light of all these results, our study supports the conclusion in the relevant literature that homocysteine contributes to neurodegeneration.

We recommend that homocysteine levels be taken into consideration during diagnosis and treatment, and underlying causes be thoroughly investigated before labeling hyperhomocysteinemia as a side effect. Furthermore, we believe that the disease progression can be slowed down with vitamin B12 and folate supplements.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gizem Gürsoy, Gülbün Asuman Yüksel;* ***Designed:*** *Gizem Gürsoy;* ***Supervision/Consultancy:*** *Gülbün Asuman Yüksel, Hülya Tireli;* ***Data Collection and/or Processing:*** *Yılmaz Çetinkaya;* ***Analysis and/or Interpretation:*** *Gizem Gürsoy, Gülbün Asuman Yüksel;* ***Source Search:*** *Gizem Gürsoy, Buse Rahime Hasırcı Bayır;* ***Article Writing:*** *Gizem Gürsoy, Gülbün Asuman Yüksel;* ***Critical Review:*** *Hülya Tireli, Buse Rahime Hasırcı Bayır;* ***Resources and Funding:*** *Gülbün Asuman Yüksel, Gizem Gürsoy;* ***Ingredients:*** *Gizem Gürsoy.*

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