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RESEARCH

PARKINSON'S DISEASE: IS IT ACTUALLY AN INFLAMMATORY DISORDER?

Abstract

Introduction: Parkinson's disease is the second leading neurodegenerative disease worldwide; however, its pathogenesis remains unclear. Recently, the neuroinflammation theory, one of the theories explaining the pathogenesis of Parkinson's disease, has become prominent. We investigated the relationship between Parkinson's disease and inflammatory markers including epicardial adipose tissue thickness, neutrophil-lymphocyte ratio, and thrombocyte-lymphocyte ratio.

Materials and Method: Seventeen patients with Parkinson's disease and 21 healthy individuals (control group) were enrolled. All the patients were evaluated by a neurologist using the Unified Parkinson's Disease Rating Scale and Hoehn and Yahr staging scale. A cardiologist measured epicardial adipose tissue thickness using echocardiography. After routine laboratory analyses, neutrophil-lymphocyte and thrombocyte-lymphocyte ratios were calculated for each patient.

Results: Both epicardial adipose tissue thickness and thrombocyte-lymphocyte ratio were higher in the patient group than in the control group, but the difference was significant only for the former. Epicardial adipose tissue thickness was significantly correlated with the scores of 2nd and 3rd sections of the Unified Parkinson's Disease Rating Scale, which evaluate activities of daily living and motor functions, respectively, and with the total Unified Parkinson's Disease Rating Scale score. Inflammatory marker evaluation according to the disease stage based on the Hoehn and Yahr staging scale revealed a significant difference in epicardial adipose tissue thickness between stage 1 and stage 2 patients. Moreover, there was a significant correlation between disease duration and thrombocyte-lymphocyte ratio.

Conclusion: Our results support the hypothesis that inflammation plays a role in the pathogenesis of Parkinson's disease.

Keywords: Parkinson disease; Inflammation; Echocardiography

ARAŞTIRMA

PARKİNSON HASTALIĞI; GERÇEKTE İNFLAMATUAR BİR HASTALIK MI?

Öz

Giriş: Parkinson hastalığı, dünya üzerinde ikinci en sık görülen nörodejeneratif hastalıktır; buna rağmen patogenezi halen aydınlanmış değildir. Parkinson hastalığı patogenezini aydınlatan teorilerden biri olan nöroinflamasyon teorisi son yıllarda ön plana çıkmıştır. Bu çalışmada Parkinson hastalığı ile epikardiyal yağ dokusu kalınlığı, nötrofil lenfosit oranı ve trombosit lenfosit oranı gibi inflamatuar göstergeler arasındaki ilişki araştırılmıştır.

Gereç ve Yöntem: Çalışmaya 17 parkinson hastası ve 21 sağlıklı birey (kontrol grubu) dahil edildi. Hastaların tümüne nöroloji uzmanı tarafından Birleşik Parkinson Hastalığı Değerlendirme Ölçeği ve Hoehn Yahr Evrelemesi yapıldı. Kardiyoloji uzmanı tarafından ekokardiyograji ile epikardiyal yağ dokusu kalınlığı ölçümü yapıldı. Tüm hastalardan rutin laboratuvar tetkikleri yapıldıktan sonra nötrofil lenfosit oranı ve trombosit lenfosit oranı hesaplandı.

Bulgular: Hem epikardiyal yağ dokusu kalınlığı hem de trombosit lenfosit oranı Parkinson grubunda kontrol grubuna göre anlamlı olarak yüksekti ancak aradaki fark sadece ilki için anlamlıydı. Epikardiyal yağ dokusu kalınlığının Birleşik Parkinson Hastalığı Değerlendirme Ölçeği'nin günlük yaşam aktivitelerini yansıtan ikinci parçası ve motor fonksiyonları yansıtan üçüncü parçası ile Hoehn Yahr Evrelemesi arasında anlamlı ilişki saptandı. Bu ilişki özellikle Hoehn Yahr Evrelemesi'ne göre Evre-1 ile Evre-2 arasında belirgindi. Ayrıca hastalık süresi ile trombosit lenfosit oranı arasında anlamlı ilişki vardı.

Sonuç: Elde ettiğimiz sonuçlar Parkinson Hastalığı patogenezinde inflamasyonun rol aldığı hipotezini desteklemektedir.

Anahtar sözcükler: Parkinson hastalığı; İnflamasyon; Ekokardiyografi

INTRODUCTION

Parkinson's disease is a chronic, progressive neurodegenerative disease involving the loss of dopaminergic neurons in the substantia nigra pars compacta of the brain and the formation of inclusion bodies, called alpha-synucleins, in the remaining cells. The reported prevalence of this disease is around 1% among individuals aged above 55 years (1), and although its etiology remains unclear, a combination of environmental and genetic factors is thought to play a role in its pathogenesis. Oxidative stress, mitochondrial dysfunction, and neuroinflammatory mechanisms (2), along with microglia- and reactive astrocyte-mediated inflammation, play a critical role in the pathogenesis of Parkinson's disease (3).

Neutrophil, lymphocyte, and thrombocyte counts can be easily detected via complete blood count analysis. Rapidly accumulated neutrophils in the infected or inflamed area account for a substantial proportion of the circulating immune cells. Both neutrophil-lymphocyte ratio (NLR) and thrombocyte-lymphocyte ratio (TLR) are considered important markers of systemic inflammation (4), and both have been reported to be high in patients with Parkinson's disease (5).

Epicardial adipose tissue (EAT), which is found in the right ventricular free wall, left ventricular apex, and atrium, surrounds the subepicardial branches of the coronary arteries. This structure is in fact a complex endocrine organ thought to play a role in the development of coronary atherosclerosis. Biopsy studies have demonstrated that EAT contains plenty of inflammatory mediators such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α) (6). Magnetic resonance imaging (MRI) was considered the best method to measure EAT thickness (EATT); however, Lacobellis et al. (7) introduced echocardiographic measurements for the first time. The echocardiographic measurements of EATT have shown a high correlation with the measurements obtained using MRI (8). A relation between EATT and inflammation has been clearly revealed by the recent studies (6,9).

We aimed to determine the relation between Parkinson's disease and inflammatory markers NLR, TLR, and EATT and to investigate the relationship of these markers with disease stage and duration.

MATERIALS AND METHOD

We included 17 patients diagnosed with idiopathic Parkinson's disease and followed in the Movement Disorders Polyclinic from January 2016 through August 2016 and 21 healthy individuals as a control group. The diagnosis of Parkinson's disease was based upon the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (10). Imaging procedures were performed in all the patients, and the potential causes for secondary Parkinsonism were excluded. Detailed physical and neurological examinations were performed in all the patients and controls, and their medical histories and demographic characteristics were recorded. Individuals with autoimmune, neoplastic, or inflammatory diseases that are likely to influence inflammatory marker levels; those with uncontrolled diabetes mellitus or hypertension; those with impaired thyroid function tests; those with hepatic or renal insufficiency; those who had experienced myocardial infarction or undergone surgical procedures in the last 3 months; those with coronary artery disease or atrial fibrillation; those with significant infection at presentation or until 7 days earlier; those with signs of infection documented by physical examination and laboratory analyses; and those having an axillary temperature >37.5°C were excluded from the study. Individuals in the control group had no documented Parkinson's disease or any other neurodegenerative disorder. This study was conducted in accordance with the World Medical Association Declaration of Helsinki, and written informed consent was obtained from each participant.

Echocardiography measurements were performed by a cardiologist in all the participants

on the free wall of the right ventricle during the simultaneous contraction of both ventricles. EATT was determined by calculating the arithmetical mean of the three maximum measurements of the short- and long-axis thicknesses from a section close to one-third of the basal part of the ventricle. Participants for whom unclear images were obtained were excluded. Furthermore, routine laboratory analyses were performed in all the participants and NLR and TLR were calculated.

Disease staging was based on the Hoehn and Yahr staging (HYS) scale, and clinical severity was graded using the Unified Parkinson's Disease Rating Scale (UPDRS). UPDRS was developed in 1987 by Fahn, Elton, and the members of UPDRS Development Committee; it comprises four sections and evaluates mental status, activities of daily living, motor functions, and treatment complications (11). The scale includes a total of 42 items, each rated between 0 and 4. The 1st section of the scale (UPDRS-1) comprises items related to mentation, behavior, and mood; the 2nd section (UPDRS-2) comprises activities of daily living; the 3rd section (UPDRS-3) comprises motor examination; and the 4th section (UPDRS-4) comprises treatment complications. High scores indicate a poor status [11]. The HYS scale is a system developed in 1967 by Hoehn and Yahr that allows both the patients and clinicians to easily define disease severity and assess disease progression (12). This study was approved by Bursa Regional Ethics Committee.

Statistical analysis

Data analyses were performed using IBM SPSS Statistics 21 program (IBM Corp., Armonk, NY, USA). Normal distribution of the variables was analyzed using Shapiro–Wilk test. Comparisons between two independent groups were performed using independent sample t-test for normally distributed variables and Mann–Whitney U test for non-normally distributed variables. Multiple-group comparisons (three or more groups) were performed using one-way analysis of variance for normally distributed variables and Kruskal–Wallis test for non-normally distributed variables. Normally distributed variables were expressed as mean±standard deviation and non-normally distributed variables as median and range (minimum and maximum). Pearson's chi-square test was used to compare categorical variables, which were expressed as numbers and percentages. Relationships between variables were analyzed using Spearman's correlation coefficient. The significance level was determined as $p<0.05$.

RESULTS

The study participants included 17 patients with Parkinson's disease (10 females and 7 males; mean age: 65.06±6.38 years) and 21 healthy subjects (control group; 14 females and 7 males; age: 62.29±5.77 years). There was no difference between the groups in terms of age, gender, and body mass index (BMI). Furthermore, no significant difference was found between the groups regarding serum glucose levels or systolic and diastolic blood pressures. The mean EATT was significantly higher in the patient group than in the control group (0.39±0.10 vs. 0.29±0.10 cm; $p=0.004$); the median TLR was also higher in the patient group than in the control group (113.79 vs. 107.07; however, the difference was not significant ($p=0.772$). The median NLR was similar in both the groups. Between-group comparisons are summarized in Table 1.

Within the patient group, correlation analysis between the UPDRS scores and inflammatory markers revealed EATT to be significantly correlated with the total UPDRS score ($r=0.581$, $p=0.014$) and with the UPDRS-2 and -3 scores ($r=0.657$, $p=0.004$ and $r=0.586$, $p=0.013$, respectively). The relationship between the UPDRS scores and the inflammatory markers in the patient group is summarized in Table 2.

The correlation analysis between disease duration and inflammatory markers in the patient group (Table 3) revealed a significant correlation only between disease duration and TLR ($r=0.780$, $p<0.001$).

Table 1. Group comparisions on evaluated parameters.

Parameter	Patient Group	Control Group	p
	(n=17)	(n=21)	
Age, years	65.06±6.38	62.29±5.77	0.169
Gender			
Female	10 (58.8)	14 (66.7)	
			0.618
Male	7 (41.2)	7 (33.3)	
BMI, kg/m2	31.09±5.91	29.52±3.64	0.324
SBP, mmHg	130.00±16.95	128.10±17.21	0.735
DBP, mmHg	70 (60–90)	70 (60–90)	0.862
EATT, cm 0.39±0.10 0.29±0.10 0.008			
Smoking			
Yes	16 (94.1)	17 (81)	
			0.355
No	1 (5.9)	4 (19)	
WBC	7.44±1.48	6.64±3.09	0.368
TLR	113.79 (61.29–227.50)	107.07 (49.86–404.28)	0.772
NLR	2.03 (1.23-4.00)	2.04 (0.95-7.14)	0.750
Glucose	103 (86-329)	101 (71-145)	0.416
Hemoglobin	13.66±1.39	14.11±1.69	0.383

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; EATT, epicardial adipose tissue thickness; WBC, white blood cell; TLR, thrombocyte-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio Data are presented as mean±standard deviation, median (minimum–maximum), or number (percentage), as appropriate.

Table 2. Results of the correlation analysis between the Unified Parkinson's Disease Rating Scale (UPDRS) scores and inflammatory markers in the patient group.

	NLR		TLR		EATT	
	r	p	r	p	r	p
UPDRS-1	-	0.847	-	0.212	-	0.185
UPDRS-2	-	0.275	-	0.490	0.657	0.004
UPDRS-3	-	0.365	-	0.911	0.586	0.013
UPDRS-4	-	0.162	-	0.414	-	0.597
UPDRS-Total	-	0.200	-	0.522	0.581	0.014

NLR neutrophil-lymphocyte ratio; TLR, thrombocyte-lymphocyte ratio; EATT, epicardial adipose tissue thickness.

Table 3. Results of the correlation analysis between disease duration and inflammatory markers in the patient group.

		NLR	TLR	EATT
Disease Duration	r	-	0.780	-
	p	0.090	<0.001	0.698

NLR, neutrophil-lymphocyte ratio; TLR, thrombocyte-lymphocyte ratio; EATT, epicardial adipose tissue thickness

DISCUSSION

Although Parkinson's disease is the second leading neurodegenerative disease worldwide, its etiology remains unclear. According to the neuroinflammation theory, which has been recently dwelled on, microglia are activated and transformed into an M1 phenotype by aging, protein aggregates, genetic mutations, environmental factors, and cytokines released from T cells. Nitric oxide and superoxide radicals, which are released from the astrocytes activated by pro-inflammatory mediators secreted from M1 microglia, cause degeneration of dopaminergic neurons, releasing products that trigger an inflammatory response through activation of glial cells. In some stages of Parkinson's disease, microglia can transform into an activated M2 phenotype, which plays a neuroprotective role in Parkinson's disease by releasing anti-inflammatory factors such as tumor growth factor-beta. The microglia- and reactive astrocyte-mediated inflammation plays a critical role in the pathogenesis of Parkinson's disease (3).

Epicardial adipose tissue exerts a cardioprotective effect under physiological conditions; however, under pathological conditions, it causes the release of pro-inflammatory cytokines, thus, affecting the heart and coronary arteries. The mechanism underlying the impairment of this balance remains unclear (13). A previous study comparing the expression of inflammatory mediators in the epicardial and subcutaneous adipose tissues revealed that among the inflammatory cytokines, IL-1β, IL-6, and TNF-α levels were higher in EAT (6).

The levels of nuclear factor-ĸB (NF-ĸB) and c-jun N terminal kinase (JNK), which play a key role in inflammation, have been found to be significantly higher in EAT samples. Furthermore, Toll-like receptor (TLR) 2 and TLR4 expression, which is considered as a strong evidence of the presence of activated macrophages, has also been found to be higher in EAT samples. All these data reveal that macrophages, JNK, and NF-ĸB play an important role in the inflammation in EAT (14).

Epicardial adipose tissue is thought to be affected by many factors, and EATT has been found to be correlated with age, BMI, blood pressure alterations, and NLR (15). Varying results have been reported regarding the correlation of EATT with age. Although most autopsy studies have found no correlation between EATT and age, some of them have demonstrated a lower EATT in young individuals (16). Moreover, no significant relationship has been reported between age and EATT measured using echocardiography (17). In this study, no significant difference was found between the patient and control groups in terms of age, BMI, and blood glucose and blood pressure levels. EATT, which is an accepted inflammatory marker, was significantly higher in the patient group than in the control group.

Research into inflammatory markers is usually based on quantification of NLR and TLR as these are easily measurable and computable. NLR is also considered as an important marker of systemic inflammation (4,18-20), whereas TLR has been demonstrated as a potential inflammatory marker in cardiac, oncologic, and rheumatologic diseases (4,21-23). NLR and TLR, which have been studied in

several inflammatory diseases, have been found to be high in patients with Parkinson's disease (5). In this study, although not significant, TLR was found to be higher in the patient group than in the control group; however, NLR was found to be similar in both the groups.

An NLR of ≥2.25 has been accepted as predictive of the presence of Parkinson's disease. Carcinoembryonic antigen, which is used to demonstrate gastrointestinal system inflammation, has not been determined to be related with disease duration, age, and HYS in patients with Parkinson's disease (5). In this study, NLR was determined to be 2.18 in the patients with Parkinson's disease. Significant correlations were found between TLR and disease duration ad well as between EATT and HYS.

The neuroinflammatory theory is supported by various studies evaluating high-sensitive C-reactive protein (CRP) levels (5, 24-25). Because CRP has been frequently studied in the earlier studies, we focused on a different inflammatory marker, i.e., EATT aiming to present a new point of view to this issue and contribute to the existing literature.

It has been demonstrated that CRP levels can rise even before the appearance of Parkinson's disease symptoms (24). Song et al. (25) failed to demonstrate a significant correlation between HYS and CRP levels; however, in this study, we demonstrated that EATT differs significantly among the patients grouped according to disease stages (stages 1–4) based on HYS. Pairwise comparisons revealed a significant difference between stage 1 and stage 2 patients, which was attributed to the fact that a substantial proportion of the patients were in the stage 1 and stage 2 groups. This result supports the hypothesis that more severe the inflammation, the more severe the disease.

In this study, EATT was found to be significantly correlated with UPDRS-2 score (which evaluates activities of daily living), UPDRS-3 score (which evaluates motor function), and total UPDRS score, indicating that increased EATT affected not only the motor prognosis but also the activities of daily living.

Our study results support the hypothesis that inflammation plays a role in the pathogenesis of Parkinson's disease. To the best of our knowledge, this is the first study investigating EATT, NLR, and TLR in patients with Parkinson's disease. Further studies with higher number of patients are required to support these results. Elucidation of the pathogenesis of Parkinson's disease, which affects millions of people worldwide, would help develop new treatment strategies in the future.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Emre M, Hanağası HA, Şahin HA, Yazıcı J. Movement Disorders. In: Öge AE, Bahar SZ (Eds). Neurology. 1st edition, Nobel press, İstanbul 2004, pp 417-47.
2. Hwang O. Role of oxidative stress in Parkinson's disease. Exp Neurobiol 2013;22(1):11-7. (PMID:23585717).
3. Wang Q, Liu Y, Zhou J. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. Transl Neurodegener 2015;4:19. (PMID:26464797).
4. Boyraz I, Koç B, Boyacı A, Tutoğlu A, Sarman H, Ozkan H. Ratio of neutrophil/lymphocyte and platelet/lymphocyte in patient with ankylosing spondylitis that are treating with anti-TNF. Int J Clin Exp Med 2014;7(9):2912-5. (PMID:25356158).
5. Akıl E et al. The increase of carcinoembryonic antigen (CEA), high-sensitivity C-reactive protein, and neutrophil/lymphocyte ratio in Parkinson's disease. Neurol Sci 2015;36(3):423-8. (PMID:25288159).
6. Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 2003;108(20):2460-6. (PMID:14581396).

7. Lacobellis G, Assael F, Ribaudo MC, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11(2):304-10. (PMID:12582228).

8. Lacobellis G, Ribudo MC, Assael F, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovasculer risk. J Clin Endocrinol Metab 2003;88(11):5163-8. (PMID:14602744).

9. Malavazos AE, Ermetici F, Cereda E, et al. Epicardial fat thickness: relationship with plasma visfatin and plasminogen activator inhibitör-1 levels in visceral obesity. Nutr Metab Cardiovasc Dis 2008;18(8):523-30. (PMID:18083357).

10. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinicopathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55(3):181-4. (PMID:1564476).

11. Fahn S, Elton RL, members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Calne CD (Eds). Recent Developments in Parkinson's Disease. Macmillan, Florham Park, New Jersey 1987, pp 153-63.

12. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967;17(5):427-42. (PMID:6067254).

13. Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. Trends Endocrinol Metab 2011;22(11):450-7. (PMID:21852149).

14. Baker AR, Harte AL, Howell N, et al. Epicardial adipose tissue as a source of nuclear factor-kappaB and c-Jun N-terminal kinase mediated inflammation in patients with coronary artery disease. J Clin Endocrinol Metab 2009;94(1):261-7. (PMID:18984670).

15. Cho KI, Heo JH, Kim HS, Im SI, Cha TJ. OS 14-09 epicardial fat thickness and neutrophil to lymphocyte ratio are increased in the non-dipper pattern. J Hypertens 2016;34 Suppl 1:e214. (PMID:27642972).

16. Tansey DK, Aly Z, Sheppard MN. Fat in the right ventricle of the normal heart. Histopathology 2005;46(1):98-104. (PMID:15656892).

17. Iacobellis G, Willens H. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr 2009;22(12):1311-9. (PMID:19944955).

18. Gökhan S, Ozhasenekler A, Mansur Durgun H, Akil E, Ustündag M, Orak M. Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack. Eur Rev Med Pharmacol Sci 2013;17(5):653-7. (PMID:23543449).

19. Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102(1):5-14. (PMID:11723675).

20. Uslu AU, Deveci K, Korkmaz S, et al. Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever? Biomed Res Int 2013;2013:185317. (PMID:23865042).

21. Wang J, Wang S, Song X, et al. The prognostic value of systemic and local inflammation in patients with laryngeal squamous cell carcinoma. Onco Targets Ther 2016;9:7177-85. (PMID:27920556).

22. Huang GY, Yang LJ, Wang XH, Wang YL, Xue YZ, Yang WB. Relationship between platelet-leukocyte aggregation and myocardial perfusion in patients with ST-segment elevation myocardial infarction after primary percutaneous coronary intervention. Heart Lung 2016;45(5):429-33. (PMID:27425196).

23. Balta S, Ozturk C. The platelet-lymphocyte ratio: A simple, inexpensive and rapid prognostic marker for cardiovascular events. Platelets 2015;26(7):680-1. (PMID:25549287).

24. Song IU, Chung SW, Kim JS, Lee KS. Association between high-sensitivity C-reactive protein and risk of early idiopathic Parkinson's disease. Neurol Sci 2011;32(1):31-4. (PMID:20532580).

25. Song IU, Kim JS, Chung SW, Lee KS. Is there an association between the level of high-sensitivity C-reactive protein and idiopathic Parkinson's disease? A comparison of Parkinson's disease patients, disease controls and healthy individuals. Eur Neurol 2009;62(2):99-104. (PMID:19521085).