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Original Article

Serum inflammation biomarkers are associated with stages of Parkinson's disease

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Abstract

Aim: The aim was to identify serum neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR) and C - reactive protein (CRP)/albumin ratio (CAR) according to disease stage in patients with idiopathic Parkinson disease (IPD).

Material and Methods: The study included 211 patients IPD diagnosis and 200 healthy individuals abiding by the exclusion criteria. Patients with Stage 4 and 5 IPD according to Modified Hoehn and Yahr (H&Y) staging were not included in the study. The control group comprised individuals in the same age interval as IPD patients, with normal neurological examinations, Mental State Examination (MMSE) score above 24 and Geriatric Depression Rating Scale (GDRS) score below 11 who abided by the exclusion criteria.

Results: For males and females in the IPD group, serum MLR, NLR and CAR were found to be high ($p<0.05$). In parallel with the disease stage of female and male IPD patients, MLR, NLR, PLR and CAR increased.

Conclusions: Our study supports the hypothesis that NLR, MLR, PLR and CAR may be associated with IPD. For identification of, and to take precautions against, chronic progressive diseases like IPD in the initial stages, it is important to identify variations in easily accessible parameters like serum NLR, MLR, PLR and CAR.

Keywords: Idiopathic Parkinson disease; inflammation; oxidative stress.

INTRODUCTION

IPD is a progressive, chronic neurodegenerative disease (1-4). The etiopathogenesis of selective loss of dopamine neurons in IPD is still uncertain. However, increasing evidence shows that oxidative stress and inflammation play an important role in degeneration of dopaminergic neurons in IPD (5-7).

For patients diagnosed with IPD, identification of inflammation and oxidative stress in the early stages and precautions taken to improve motor and cognitive problems make it possible to improve clinical outcomes of the disease and contribute to slowing progression. NLR, MLR, PLR and CAR have begun to be frequently used as indicators of inflammation and oxidative stress in recent times.

In this study, the aim was to research the role of inflammation and oxidative stress in the etiology of IPD by identifying serum NLR, MLR, PLR and CAR according to disease stage.

MATERIAL and METHODS

The study included 211 patients IPD diagnosis and 200 healthy individuals abiding by the exclusion criteria. Patients with Stage 4 and 5 IPD according to H&Y staging were not included in the study. The control group comprised individuals in the same age interval as IPD patients, with normal neurological examinations, MMSE score above 24 and GDRS score below 11 who abided by the exclusion criteria.

In the IPD and control groups, those with chronic disease, presence of abnormal cranial imaging findings, smoking and alcohol habits, infectious disease history, obesity, diseases causing increased CAR levels and patients using corticosteroid medication were not included in the study.

The patient and control groups had the MMSE and GDRS administered. Additionally, every patient had UPDRS and H&Y administered to determine IPD stage. The disease duration, cognitive and motor functions (UPDRS) and disease stage (H&Y) were assessed related to the disease (4,11,12).

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Collection of samples and obtaining serum

Blood samples taken for analysis were obtained from outpatients attending our hospitals. Samples were taken after nearly 12 hours of fasting, between 08:00 and 12:00 in the morning. To obtain serum, separator gel tubes were used, while potassium-EDTA tubes were used for blood counts. Separator gel tubes were sent to the laboratory in appropriate conditions and centrifuged for 10 minutes at 5000 rpm after being left for 20 minutes to separate the serum.

Albumin, CRP, urea and creatinine tests were completed in our laboratory using a Cobas 8000 series c702 modular analyzer in a closed system with spectrophotometric measurement. The device used kits obtained from the company. The calibration for the kits was performed with calibrators obtained from the same company and quality control was ensured with control serum.

Blood counts (hemogram) were obtained using a XN-1000 device in our laboratory. This device is a closed-system analyzer using Fluorescence Flow Cytometry for measurement in all modes. The device used kits obtained from the company. The calibration for the kits was performed with calibrators obtained from the same company and quality control was ensured with control serum.

Statistical Analysis

The statistic SPSS 25.0 program was used for statistical analysis of data. Continuous measurements are given as mean and standard deviation. The Mann-Whitney U test was used for comparison of numerical values in two groups for samples without normal distribution, while the independent samples t test was used for samples with normal distribution. Comparison of numerical values in three groups used the Kruskal-Wallis test for data with non-normal distribution and the one-way ANOVA test for samples with normal distribution. All tests had statistical significance level taken as $p<0.05$.

RESULTS

In our study, there were 101 healthy women in the control group and mean age was 74.119±3.235 years. The MLR, NLR, PLR and CAR were 0.178±0.058; 1.555±0.395; 113.556±23.567; and 0.046±0.035, respectively. In the IPD group, there were 110 female patients and mean age was 73.809±4.845 years. The MLR, NLR, PLR and CAR were 0.225±0.062; 2.173±0.511; 132.661±19.958 and 0.094±0.054, respectively. There were significant differences identified for all parameters, apart from age, between females in the control and IPD groups ($p>0.05$). In the IPD group, the MLR, NLR, PLR and CAR were found to be statistically high ($p<0.05$) (Table 1).

In our study, there were 99 healthy males in the control group and mean age was 73.717±3.133 years. The MLR, NLR, PLR and CAR were 0.157±0.066; 1.713±0.5; 113.462±25.024; and 0.044±0.033, respectively. In the IPD group, there were 101 male patients and mean age was 73.327±4.364 years. The MLR, NLR, PLR and CAR were 0.224±0.065; 2.28±0.551; 128.894±19.803; and 0.1±0.105, respectively. There were significant differences identified for all parameters between males in the control and IPD groups, apart from age ($p>0.05$). In the IPD group, the MLR, NLR, PLR and CAR were found to be statistically high ($p<0.05$) (Table 1).

There were significant differences between females and males according to disease stage for all parameters ($p<0.05$) (Table 2).

As the disease stage progressed for females and males, age, disease duration, UPDRS points, MLR, NLR, PLR and CAR displayed a statistically significant level of increase ($p<0.05$) (Table 2).

Table 1. Data for females and males in the control and IPD groups

Gender	Control		IPD		P-Values
	N	Mean±Std.dev	N	Mean±Std.dev	
Females					
Age	101	74.119±3.235	110	73.809±4.845	0.887
MLR	101	0.178±0.058	110	0.225±0.062	0.000
NLR	101	1.555±0.395	110	2.173±0.511	0.000
PLR	101	113.556±23.567	110	132.661±19.958	0.000
CAR	101	0.046±0.035	110	0.094±0.054	0.000
Males					
Age	99	73.717±3.133	101	73.327±4.364	0.737
MLR	99	0.157±0.066	101	0.224±0.065	0.000
NLR	99	1.713±0.5	101	2.28±0.551	0.000
PLR	99	113.462±25.024	101	128.894±19.803	0.000
CAR	99	0.044±0.033	101	0.1±0.105	0.000

Statistical significance level $p<0.05$

Table 2. Data for male and female IPD cases according to stage

Gender	Stage 1		Stage 1.5		Stage 2		Stage 2.5		Stage 3		P-Values
Females	N	Mean±Std.Dev	N	Mean±Std.Dev	N	Mean±Std.dev	N	Mean±Std. dev	N	Mean±Std.dev	
Age	20	68.85±4.056	21	70.81±3.516	23	73.652±2.707	19	76±3.844	27	78.407±2.965	0.000
DD (years)	20	2.1±0.788	21	3.476±0.928	23	5.522±0.947	19	7±1.333	27	10.148±2.248	0.000
UPDRS	20	26.45±4.058	21	37±3.924	23	49.522±4.981	19	60.368±6.954	27	78.741±5.749	0.000
MLR	20	0.162±0.051	21	0.187±0.047	23	0.237±0.028	19	0.236±0.035	27	0.285±0.053	0.000
NLR	20	1.666±0.264	21	1.844±0.207	23	2.224±0.374	19	2.282±0.372	27	2.686±0.477	0.000
PLR	20	120.047±19.33	21	113.388±12.377	23	135.241±14.198	19	140.184±12.772	27	149.503±15.208	0.000
CAR	20	0.037±0.021	21	0.065±0.029	23	0.103±0.039	19	0.126±0.057	27	0.13±0.049	0.000
Males											
Age	21	69.095±4.23	22	71.909±2.893	19	73.368±2.813	20	75.55±2.819	19	77.263±3.827	0.000
DD (years)	21	1.952±0.921	22	3.909±0.868	19	5.632±0.761	20	7.2±0.894	19	9.368±1.422	0.000
UPDRS	21	26.952±4.153	22	37.682±5.349	19	48.526±3.747	20	55.5±5.021	19	75.632±6.542	0.000
MLR	21	0.161±0.033	22	0.192±0.05	19	0.23±0.048	20	0.246±0.041	19	0.303±0.048	0.000
NLR	21	1.741±0.301	22	2.067±0.299	19	2.153±0.327	20	2.443±0.338	19	3.077±0.374	0.000
PLR	21	106.865±15.184	22	127.071±15.214	19	129.688±15.604	20	137.755±16.887	19	145.229± 12.969	0.000
CAR	21	0.055±0.026	22	0.079±0.036	19	0.137±0.211	20	0.096±0.051	19	0.14±0.071	0.000

Statistical significance level p<0.05, DD: disease duration

DISCUSSION

Hemogram and biochemical studies are easily accessible, simple and cheap tests providing significant data about quantitative and qualitative characteristics of a variety of blood cells including platelets, neutrophils, monocytes, lymphocytes, CRP and albumin levels. PLR, MLR, NLR and CAR were determined to be prognostic and potential inflammatory markers for chronic neurological diseases. These are more accessible parameters when compared to other inflammatory cytokines including IL-6, IL-1β, and TNF-α (13-17).

Neuroinflammation is associated with many neurological disorders (18). PLR, MLR and NLR levels were defined as inflammation biomarkers in different diseases (14-16,19). NLR has been commonly used as an inflammation marker and indicator of prognosis for a variety of disorders (20,21).

Akıl et al. in a study of 51 PD patients and 50 healthy controls reported the CRP and NLR levels were significantly higher in PD patients than normal controls (13). Among Parkinson patients, NLR was found to be significantly high compared to age- and sex-matched healthy controls (22). Uçar et al. in a study of 46 IPD patients and 60 healthy controls did not identify any significant differences between the groups in terms of serum NLR values (23). Rembach et al., in a study assessing the diagnostic benefit of long-term measurements of NLR, identified that NLR was higher in AD cases compared to a control group and reported a significant correlation between NLR and cognitive insufficiency (24). Kalelioğlu et al. in a 2017 study compared the NLR and PLR values in AD and MCI patients and found the NLR values were significantly high in the AD and MCI groups compared to the control group. The same study reported no correlation between AD and MCI diagnosis with PLR values (25). Huang et al. showed patients with Guillain-Barre syndrome had higher NLR and MLR levels than healthy controls (19). Özdemir et al. reported that serum albumin levels were significantly low among patients with convulsive status epilepticus and that NLR was significantly high in the acute period (26). Similarly, increasing PLR has been shown for use in determining bad prognosis in acute stroke and cancer patients (21,27). High NLR was shown to be an independent variable associated with symptomatic carotid artery plaques (28). Studies by Akboğa et al. found the PLR and NLR levels were high in patients with cerebral venous sinus thrombosis compared to a control group and reported that these parameters may be used as thrombo-inflammatory markers (29). Bisgaard et al. identified that NLR levels were high in multiple sclerosis and optic neuritis patients compared to controls (30). Yang et al. stated that high NLR was a simple and useful potential marker to indicate disease activity in MG patients (31). Karabulut et al. found that NLR was higher during migraine attacks compared to a control group (32).

CRP is not only a biomarker for chronic inflammation, at this same time it plays a direct participatory role in the pathologic process (33,34). Homocysteine, UA, albumin and bilirubin are described as laboratory parameters linked to oxidative stress (9,20). CRP levels are shown to increase in chronic diseases (33,35-39). Elevated CRP was previously reported to be correlated with bad prognosis for patients with ischemic stroke (40).

To the best of our knowledge, our study is the first to assess serum NLR, PLR, MLR and CAR in IPD patients according to disease stage and gender. Generally, all data in our study comply with the literature. In our study, it was thought that the levels of MLR, NLR, PLR and CAR represent independent parameters in parallel with the increase in disease stage in women and men with IPD.

The most important limitation of our study is that the patient and control groups were not assessed in terms of anthropometric and nutritional characteristics, whether they exercised regularly and possible effects of medications used within the scope of the study. Additionally, the relatively small size of the sample is another limitation.

CONCLUSION

Recommendations

Peripheral inflammation biomarkers can be meaningful in patients with Parkinson disease for the early detection, and preventing the motor, autonomic, cognitive and behavioral symptoms of the disease.

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