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Relationship Between BDNF and LPS Levels in the Blood of Patients with Different Neurological Diseases: A Small Cohort Study

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ABSTRACT

Objective: Neuroinflammation and blood-brain barrier (BBB) dysfunction are key factors in various neurological disorders, disrupting brain tissue balance and leading to neuronal death. BBB integrity decline is evident in Alzheimer's Disease (AD), Parkinson's Disease (PD), Multiple Sclerosis (MS), and epilepsy.

Materials and Methods: We measured levels of lipopolysaccharide (LPS), the largest endotoxin, and brain-derived neurotrophic factor (BDNF) in patients' blood plasma and correlated them with biochemical parameters to identify biomarkers for these diseases.

Results: Significant associations were observed between LPS, C-reactive protein (CRP), BDNF, and lactate dehydrogenase (LDH) levels across conditions. LPS was positively correlated with CRP levels in epilepsy ($r=0.753$, $p=0.002$). Additionally, BDNF was negatively correlated with CRP in PD patients ($r=-0.53$, $p=0.042$). Moreover, a negative correlation was found between LPS and LDH in AD patients ($r=-0.521$, $p=0.047$).

Conclusion: Our findings correspond to the etiology of neuroinflammation involved in the pathophysiology of relevant diseases and suggest the potential use of these biomarkers in the early diagnosis and monitoring of neurological diseases, guiding future research towards better patient outcomes and therapies.

Keywords: Brain-derived neurotrophic factor, lipopolysaccharide, neuroinflammation, neurological diseases, biomarker

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INTRODUCTION

The molecular origins of most neurological diseases and disorders are still largely obscure. However, most previous studies have shown that neuroinflammation and blood-brain barrier (BBB) dysfunction are at the root of a wide variety of neurological disorders and are associated with disease progression (1, 2). Although the inflammatory response process in the central nervous system (CNS) might play an active role in the healing of damaged tissue, irregular inflammatory processes have been shown to disrupt homeostasis of brain tissue and cause neuronal death (3).

The most important component of the clinical picture of neuroinflammation-mediated neurodegeneration is the deterioration of BBB structure and function (4). According to the findings obtained from the studies, BBB integrity was impaired and the neurovascular unit structure was destroyed in neurodegenerative diseases such as Alzheimer's Disease (AD) (5), Parkinson's disease (PD) (6), Multiple Sclerosis (MS) (7), and epilepsy (8). In this context, lipopolysaccharide (LPS), the largest endotoxin, may be an important tool for evaluating the neuroinflammation and BBB integrity axis. Briefly, when bacteria die, endotoxins are generally released, creating an antigenic effect that stimulates myeloid cells and initiates the neuroinflammation process, respectively (9, 10). For instance, studies on the endotoxin hypothesis in neurodegeneration have shown that LPS, which is excessively produced by intestinal gram-negative bacteria, has a significant effect on inflammation that triggers the accumulation of Aß plaques and tau fibrils in the pathogenesis of AD (11). Although LPS is normally too large to cross the BBB, localized LPS findings with Aβ plaques in AD brains are related to disease-induced BBB permeability in neurological processes (12). These findings support the relationship between the leaky gut barrier and the leaky BBB, which leads to neurological diseases by disrupting brain homeostasis via LPS (13).

Brain-derived neurotrophic factor (BDNF) is a widely distributed neurotrophin in the brain that is involved in many critical processes, from plasticity to neuronal survival and dendritic branching (14). Because of this versatile function, changes in BDNF levels in many neuropathological conditions have been examined in most previous studies to obtain important clues regarding the disease process. Therefore, alterations in BDNF levels may be used as a biomarker for neurological diseases (15). In the current study, we aimed to compare LPS and BDNF levels in the blood plasma of patients with different neurological diseases, such as AD, PD, MS, and epilepsy. In addition, we aimed to contribute to the pathophysiology of neurological diseases by correlating our findings with various biochemical parameters of patients.

MATERIALS AND METHODS

Patients

The study groups consisted of sixty patients (AD, n=15; PD, n=15; MS, n=15; and epilepsy, n=15) and 15 healthy individuals (control group) were recruited from the Department of Neurology in Bezmialem Vakif University Hospital, Istanbul, Turkiye. The study was approved by the Bezmialem Vakif University Research Ethics Committee (07.06.2017, No:12/27; 05/07.2017, No:14/18; 10.07.2020, No:08/117; 10.03.2021, No:3/11) and informed consent was obtained from all participants. In addition, this study was conducted in accordance with the ethical principles of the Declaration of Helsinki. According to the power analysis based on the findings from the post-hoc analysis, assuming a difference of 5.07 between means and a pooled standard deviation of 10, the required sample size at a 95% confidence level was determined to be n1=n2=n3=n4=n5=15, with a total of n=75, achieving a study power of 85%.

Sample Collection

Peripheral blood samples from patients and controls were transported to the laboratory via cold chain transport with EDTA tubes. Blood samples were centrifuged for 10 min at 10,000 g and 4°C to obtain plasma. The obtained plasma was then aliquots and stored at -80°C until further experiments.

Biochemical Measurements

Demographic and clinical characteristics, medication use, and biochemical variables of the patients were obtained from hospital records. Blood sampling for C-reactive protein (CRP) and other biochemical parameters (the levels of creatinine, lactate dehydrogenase (LDH), calcium, potassium, and sodium) was performed using the same blood sample used in the determination of BDNF and LPS levels. CRP was analyzed using a turbidimetric method. Biochemical measurements were performed using standard clinical laboratory methods with certified assays at the Bezmialem Vakif University Hospital clinical laboratory.

Determination of Protein Levels by Enzyme-Linked Immunosorbent Assay

Plasma samples stored at -80^{0}C were taken on ice, and necessary dilutions were performed for optimization of the kits. LPS levels were analyzed using an enzyme-linked immunosorbent assay (ELISA) Kit for Human Lipopolysaccharides (MyBioSource, Inc., San Diego, CA, USA) according to the manufacturer's instructions. BDNF levels were analyzed with Uncoated Human BDNF ELISA Kit (Elabscience, Memorial Drive, Suite 108, Houston, Texas, USA). The LPS and BDNF levels in the last step were determined using absorbance at 450 nm with a Multiskan GO microplate reader (Thermo Fisher Scientific, Boston, MA, USA).

Statistical Analyses

In this study, data distribution was examined using the Shapiro-Wilk test. Comparisons of non-normally distributed data between 5 independent groups were performed using the Kruskal–Wallis (K-W) test. Post hoc comparisons were made using the Dunn test. In all pairwise comparisons, significance values were adjusted using the Bonferroni correction for

multiple tests. Descriptive statistics of numerical data were presented with median (min-max) according to distribution. Categorical data were represented by frequency (percentage). The correlations of relevant biochemical parameters with LPS and BDNF levels were calculated using Pearson's correlation coefficient. All statistical analyses were performed and reported in IBM SPSS Statistics 26.0 programme at 0.05 significance level and 95% confidence level.

Table 1. Demographic and biochemical data of the participants.

	Control	Epilepsy	Alzheimer's Disease	Parkinson's Disease	Multiple Sclerosis	p-value
Gender (Female / Male)	10/5	12/3	6/9	9/6	11/4	0.189#
Age years, mean ± SD	28.40 ± 4.014	33.87 ± 12.438	75.60 ± 6.663	65.73 ± 9.316	37.27 ± 10.333	0.000
Na^+ Mean (Min.-Max.) Reference value 135-145 mmol/L	134.53 (123-143)	136.13 (128-140)	138.27 (133-142)	138.27 (135-143)	139.60 (137-143)	**0.008***
K^+ Mean (Min.-Max.) Reference value 3.5-5.1 mmol/L	6.5733 (3.67-10.00)	5.5193 (3.82-10.00)	5.1320 (3.80-10.00)	4.8653 (3.61-10.00)	4.3347 (3.81-4.72)	0.06
Ca^{++} Mean (Min.-Max.) Reference value 8.3-10.6 mg/dL	6.167 (1.0-10.0)	7.753 (1.0-10.0)	8.080 (1.2-9.8)	8.693 (1.5-10.2)	9.567 (8.8-10.4)	0.117
CRP Mean (Min.-Max.) Reference value 0-5 mg/L	4.6840 (0.20-36.80)	2.5273 (0.02-15.00)	4.7853 (0.02-33.33)	6.0640 (0.12-86.36)	0.9540 (0.19-9.18)	**0.019***
Creatinine Mean (Min.-Max.) Reference value 0.5-1 mg/dL	0.7280 (0.44-1.04)	0.7147 (0.56-1.02)	0.9653 (0.64-1.86)	1.0013 (0.73-3.25)	0.7593 (0.59-1.01)	**0.002***
LDH Mean (Min.-Max.) Reference value 122-222 U/L	164.53 (118-210)	173.47 (135-294)	208.80 (162-285)	174.93 (39-249)	180.53 (126-250)	**0.018***

CRP, C-reactive Protein; LDH, Lactate Dehydrogenase. Kruskal-Wallis Test was used to compare numerical data according to disease groups. Asterisks (*) indicate statistical significance. #Chi-Square test was used to compare

Table 2. Pairwise comparisons of diseases

	Na^+ Adj. Sig.	CRP Adj. Sig.	Creatinine Adj. Sig.	LDH Adj. Sig.
Control -Epilepsy	1.000	1.000	1.000	1.000
Control-Parkinson's Disease	1.000	0.858	1.000	1.000
Control-Alzheimer's Disease	0.613	1.000	0.202	**0.014***
Control-Multiple Sclerosis	**0.009***	1.000	1.000	1.000
Epilepsy-Parkinson's Disease	1.000	1.000	**0.014***	1.000
Epilepsy-Alzheimer's Disease	1.000	0.593	**0.037***	0.067
Epilepsy-Multiple Sclerosis	**0.032***	1.000	1.000	1.000
Parkinson's Disease-Alzheimer's Disease	1.000	**0.010***	1.000	0.370
Parkinson's Disease-Multiple Sclerosis	0.895	1.000	0.226	1.000
Alzheimer's Disease-Multiple Sclerosis	1.000	0.170	0.469	0.443

Significance values have been adjusted by the Bonferroni correction for multiple tests. The asterisk (*) in the table indicates statistical significance, $p<0.05$. Adj. Sig., Adjusted significance; CRP, C-reactive protein; LDH, lactate dehydrogenase.

RESULTS

Clinical Assessments

The study cohort consisted of 60 patients, 15 patients in each disease group (Epilepsy, AD, PD, and MS), and 15 healthy individual in the control group. According to the demographic data, 64% (n=48) of the participants were female and 36% (n=27) of them were male. The average age of all participants was 48.17 years, while the distribution within disease groups ranged from 21 to 85. The demographic data of the participants are presented in Table 1. There was a significant difference in the age of participants ($p<0.001$). Patients with AD and PD were older than the other patients and healthy controls (Table 1).

In addition, certain biochemical parameters were evaluated in the serum of patients and controls. These parameters were the levels of Na^+, K^+, Ca^{++}, Creatinine, CRP, and LDH (Table 1). According to the statistical analysis, a significant difference was found among the groups in terms of Na^+, CRP, creatinine, and LDH values ($p<0.05$). On the other hand, there was no change in the levels of K^+ and Ca^{++} with studied neurological dysfunctions ($p>0.05$).

Compared with the healthy controls, there was an increase in the levels of Na^+ and LDH in patients with neurological disease (Table 1). Post-hoc pairwise comparisons indicated that the increase in the levels of Na^+ was significant in patients with MS ($p=0.009$, Table 2). In addition, MS patients had significantly higher Na^+ levels than that of patients with epilepsy ($p=0.032$). The increase in LDH reached significant values only in the AD patients ($p=0.014$). However, these values were in the normal range.

Compared with the control group, the CRP values were decreased in the epilepsy and MS groups and were increased in the AD and PD groups (Table 1). The CRP level was significantly higher in the PD group than in the AD group, and it was out of the normal range ($p=0.010$). Lastly, the creatinine values were significantly increased in the PD and AD groups compared with the control group ($p=0.020$ and $p=0.009$, respectively). In addition, compared with the epilepsy patients, the creatinine levels were significantly increased in the AD and PD patients ($p=0.037$ $p=0.014$, respectively) (Table 1).

LPS and BDNF

According to the Kruskal-Wallis test, no significant difference was found in LPS levels among the groups. The LPS level was increased, especially in PD patients, compared with the control group (Figure 1). However, there was no change in LPS values among the other neurological disorders.

Although no significant difference was observed between the groups, serum BDNF levels were observed to be higher in the MS group than in the other groups, as shown in Figure 2, but the difference did not reach the expected significance level.

Correlation Analysis of LPS and BDNF Levels According to Biochemical Parameters

Correlations of LPS and BDNF with the levels of Na^+, K^+, Ca^{++}, CRP, creatinine, and LDH were presented in Table 3. Pearson's correlation analysis showed a statistically significant positive correlation between LPS and CRP levels of epilepsy patients ($r=0.753$, $p=0.002$). In patients with AD, LPS levels were negatively correlated with the levels of LDH ($r=-0.521$, $p=0.047$).

Table 3. Pearson's correlation of LPS and BDNF levels with biochemical parameters

	Control (n=15)		Epilepsy (n=15)		Alzheimer's Disease (n=15)		Parkinson's Disease (n=15)		Multiple Sclerosis (n=15)	
LPS correlations with	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**
Na^+ (mmol/L)	-0.357	0.191	-0.348	0.223	-0.057	0.839	0.131	0.641	0.166	0.554
K^+ (mmol/L)	0.140	0.618	0.205	0.481	0.120	0.671	0.168	0.549	0.068	0.810
Ca^{++} (mg/dL)	-0.128	0.650	0.161	0.582	-0.344	0.209	-0.171	0.542	0.252	0.366
CRP (mg/L)	0.471	0.077	0.753*	0.002	-0.502	0.056	-0.265	0.339	0.178	0.525
Creatinine (mg/dL)	-0.036	0.899	0.192	0.512	-0.131	0.643	-0.076	0.788	0.179	0.524
LDH (U/L)	0.125	0.657	0.233	0.422	-0.521*	0.047	0.456	0.088	0.232	0.405
BDNF correlations with	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**
Na^+ (mmol/L)	-0.185	0.509	-0.052	0.855	-0.498	0.059	0.159	0.571	-0.005	0.985
K^+ (mmol/L)	0.353	0.197	0.494	0.061	-0.136	0.629	0.161	0.566	-0.336	0.221
Ca^{++} (mg/dL)	-0.086	0.760	-0.085	0.763	-0.240	0.388	0.206	0.461	-0.437	0.104
CRP (mg/L)	-0.273	0.325	0.191	0.494	-0.005	0.985	-0.530*	0.042	-0.469	0.078
Creatinine (mg/dL)	0.211	0.450	-0.156	0.578	0.025	0.929	-0.023	0.934	0.063	0.825
LDH (U/L)	-0.149	0.595	-0.216	0.439	-0.172	0.541	0.479	0.071	-0.482	0.069

n is the number of individuals. Statistical evaluation using Pearson's Correlation. LPS, lipopolysaccharide; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; LDH, lactate dehydrogenase * $p<0.05$.

Table 4. Receiver operating characteristic (ROC) models for healthy controls vs. patients with epilepsy, Alzheimer's Disease, Parkinson's Disease, and Multiple Sclerosis

	Epilepsy	Alzheimer's Disease	Parkinson Disease	Multiple Sclerosis
BDNF				
AUC	0.60	0.58	0.53	0.63
Standard Error	0.119	0.113	0.112	0.103
95% Confidence Interval	0.410-0.777	0.391-0.760	0.335-0.709	0.429-0.833
p-value	0.38	0.45	0.78	0.22
Sensitivity	86.67	73.33	66.7	66.7
Specificity	60.0	60.0	40.0	60.0
Criterion	<7341.24	<7392.39	<7213.35	<7639.64
LPS				
AUC	0.58	0.67	0.69	0.59
Standard Error	0.110	0.100	0.102	0.107
95% Confidence Interval	0.384-0.760	0.476-0.831	0.495-0.844	0.384-0.803
p-value	0.45	0.08	0.06	0.38
Sensitivity	57.1	80.0	73.3	66.7
Specificity	53.3	46.7	60.0	46.7
Criterion	>564.54	>539.43	>583.76	>577.85

AUC: Area under the ROC Curve; LPS, lipopolysaccharide; BDNF, brain-derived neurotrophic factor

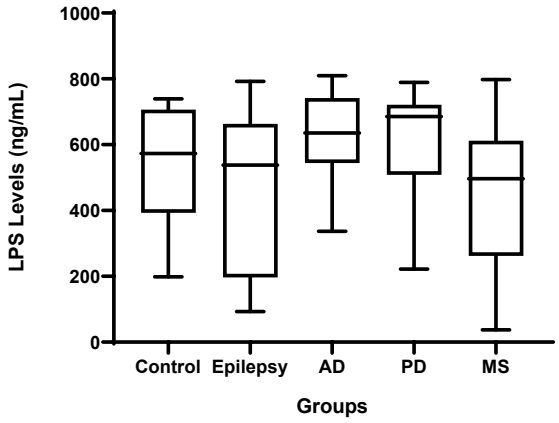

Figure 1. Distribution of LPS (ng/mL) ELISA levels by groups.

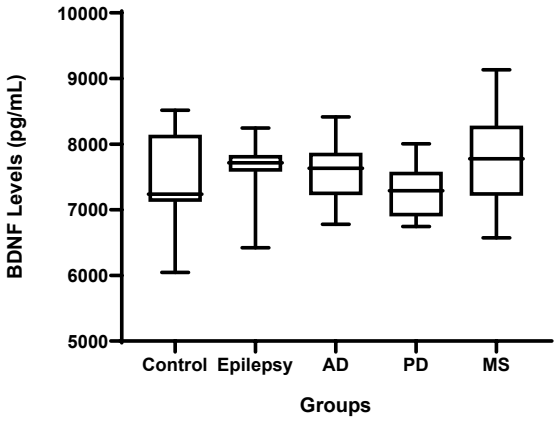

Figure 2. Distribution of BDNF (pg/mL) ELISA levels according to groups.

In addition, there was a statistically significant negative correlation between BDNF and CRP levels (r=0.53, p=0.042) in patients with PD.

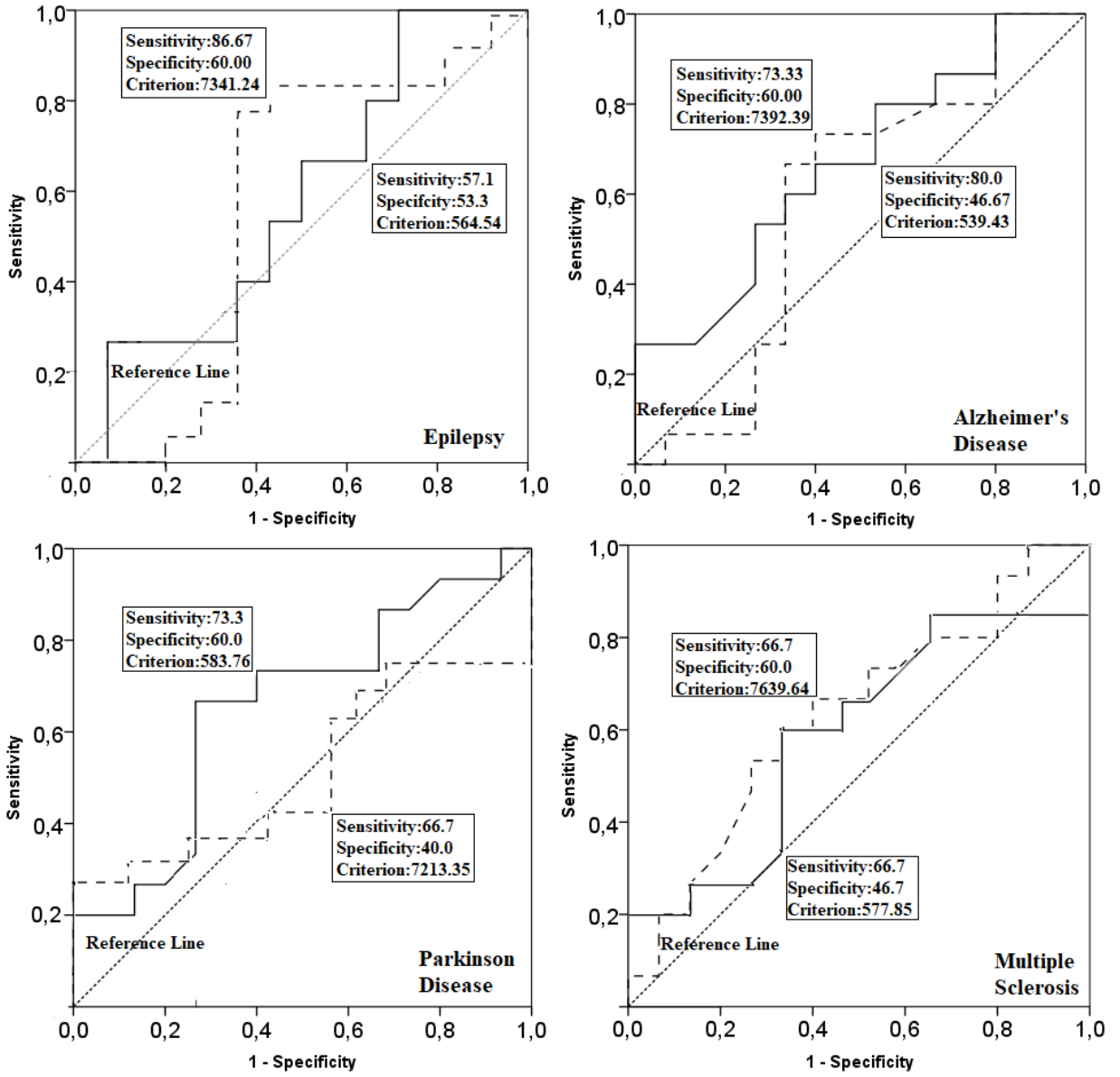

Figure 3. Receiver-operating characteristic (ROC) curves for the levels of BDNF and LPS.

Receiver Operating Characteristic (ROC) Curve Analysis of LPS and BDNF Levels for Differentiating Neurological Diseases

The levels of LPS and BDNF in epilepsy, AD, PD, and MS were analyzed by ROC curve analysis to determine the strength of the levels of LPS and BDNF in blood serum to differentiate distinct neurological diseases (Figure 3, Table 4). According to the ROC curves, the LPS levels had better sensitivity and specificity for distinguishing PD from healthy controls (Table 4). LPS>583.76 pg/mL as the cut-off value, differentiated patients with PD from healthy individuals (sensitivity 73.0%, specificity 60.0%). However, BDNF did not yield an improvement to discriminate in patients with neurological disorders and healthy individuals (Table 4).

DISCUSSION

According to the reports, the global economic and social burden of neurological diseases is increasing daily; one in every three people is affected at some point in life, and deaths due to neurological diseases have increased by 40% in the last 30 years (16, 17). Therefore, in the current study, we aimed to determine the relationships between the levels of BDNF

and LPS in blood plasma and biochemical findings regarding neuroinflammation for the early diagnosis of neurological diseases, including epilepsy, AD, PD, and MS.

In this context, LPS, which causes inflammation and metabolic changes, was examined in selected neurological disorders, and it was found that its levels were significantly increased, especially in PD, rather than in other studied neurological disorders. LPS causes a wide variety of metabolic changes when its levels increase in the blood because of bacterial infections or increased intestinal barrier permeability. An increase in blood LPS triggers the production of pro-inflammatory cytokines and initiates the inflammation process (18). The increase in LPS levels in the blood also manifests endotoxemia and increases the biomarkers of inflammation and infection such as CRP (19). In PD, we observed an increase in CRP levels parallel to an increase in LPS levels, which was also observed in previous studies (20). This outcome was based on the endotoxin hypothesis of PD, which proposes that LPS endotoxins contribute to the pathogenesis of this disorder (21).

Furthermore, we also found a statistically significant positive correlation between LPS and CRP levels in the epilepsy group. In patients with epilepsy, the CRP levels were significantly lower than the control levels. This can be related to the interaction of complement systems with each other. Previous studies have shown that dysregulation of the complement system may be related to epileptogenesis in both animal models and human studies (22). We also found a statistically significant negative relationship between plasma BDNF levels and the CRP trend in the PD group. It is emphasized in studies on PD that the infiltration of peripheral lymphocytes and neutrophils into the brain due to disruption of the integrity of the BBB or damage to the ion transport system may disrupt brain homeostasis and cause ROS production and neuroinflammation (23). The negative correlation between BDNF and CRP levels, which we found to be compatible with all of this literature, indicates that systemic metabolic processes are effective in the pathogenesis of PD and that biomarkers can be detected in serum and plasma samples via metabolomic studies. Studies have shown that CRP levels are high in patients with PD and have been described as a biomarker, particularly in the early stages of PD (24, 25). In addition, the negative relationship between CRP levels and BDNF in our patients with PD was completely consistent with the literature. Studies have shown that serum BDNF levels are significantly reduced in patients undergoing PD and in animal models (26, 27). The protective effects of BDNF are achieved through the activation of the TrkB/MAPK/ERK1/2/IP3K/Akt pathway. Activation of this pathway results in a reduction of apoptosis, as well as neurotoxicity, because molecules are released from apoptotic cells like nitric oxide (NO) (28). PD exhibits elevated levels of oxidative stress, increased NO production, and heightened apoptosis as well (29, 30). In light of these data, the increase in CRP levels, which is a parameter related to inflammation, and the decrease in BDNF, which is a neuroprotective molecule, clearly indicate neuroinflammation-related cell loss. For this reason, additional studies on a larger cohort in the future are warranted, and this negative relationship, especially serum CRP levels, may be a biomarker for the early stage of PD.

Another finding of our study was the statistically significant negative correlation between LPS levels and LDH levels in the AD group. The lactate shuttle is crucial in brain metabolism for long-term memory processes (31). LDH is responsible for the lactate-pyruvate cycle between neurons and glia in several physiological processes, but its function is not fully known (32). However, recent studies have shown that LDH is highly effective against beta-amyloid accumulation and ageing, which are components of neurodegeneration processes (33, 34). In a study conducted in rats, memory loss and learning problems in avoidance behaviour were found when the lactate mechanism in astrocytes was disrupted (35). In our study, we found that the LDH parameter was negatively correlated with LPS serum levels in patients with Alzheimer's disease. The statistically significant increase in LDH levels is consistent with the general literature on neurodegeneration and LDH (36, 37). Although additional studies and a larger cohort are needed to confirm this result, the high LDH level we obtained is associated with impaired energy metabolism in the brain, as shown in many studies related to neurodegenerative diseases and even depression (38-40).

According to the ROC analysis results, LPS levels demonstrated notable sensitivity and specificity for distinguishing Parkinson's disease from healthy controls, with a determined cut-off value of 583.76 pg/mL, achieving a sensitivity of 73.0% and specificity of 60.0%. Conversely, BDNF did not exhibit significant discriminatory power between patients with neurological disorders and healthy subjects. These findings underscore the potential of LPS as an endotoxin, in non-invasively discerning PD characterized by neurodegeneration. We propose that obtaining statistically significant results on BDNF levels could be feasible with a larger cohort.

In our study, no statistically significant differences were found between the serum LPS and BDNF levels and blood biochemical parameters in the MS group. We believe that the drugs used by patients may mask the statistical significance and affect blood parameters. We also plan to examine MS, which is a highly heterogeneous neurological disease, in a larger cohort with additional validation in future experiments.

CONCLUSION

In conclusion, our study sheds light on the intricate relationships between biomarkers and biochemical parameters in various neurological diseases, including epilepsy, AD, PD, and MS. We found significant associations between blood LPS, CRP, BDNF, and LDH levels with different neurological conditions. Specifically, our finding, supported by the positive correlation between CRP and LPS levels, suggests that CRP is an indicator of neurodegeneration in epilepsy. Additionally, although the difference between the groups was not significant, LPS levels were found to be higher in the PD group than in the

control. Moreover, the negative correlation between BDNF and CRP levels in PD patients underscores the importance of neuroprotective mechanisms in combating inflammation-associated cell loss. Additionally, the negative correlation between LPS and LDH levels in AD patients with high LDH levels suggests disrupted energy metabolism, a common feature of neurodegenerative processes. Although our study did not reveal significant differences in serum LPS and BDNF levels among patients with MS, we recognize the need for further investigation with larger cohorts to better understand the complexities of this heterogeneous disease. Overall, our findings suggest the potential utility of these biomarkers in the early diagnosis and monitoring of neurological diseases, offering avenues for future research aimed at improving patient outcomes and developing therapeutic strategies.

Ethics Committee Approval: The study was approved by the Bezmialem Vakif University Research Ethics Committee (07.06.2017, No:12/27; 05/07.2017, No:14/18; 10.07.2020, No:08/117; 10.03.2021, No:3/11).

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Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- N.D.K., B.E., E.Y.; Data Acquisition: N.D.K., B.E., S.S., C.T., A.B., F.U., G.B., A.E.G., F.A., B.S., M.Y., Z.E.; Data Analysis/Interpretation: B.E., N.D.K.; A.Y.T.; Drafting Manuscript- N.D.K., B.E.; Critical Revision of Manuscript- N.D.K., B.E.; Final Approval and Accountability- B.E.

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