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The evaluation of the inflammatory parameters in the patients with controlled epilepsy versus the patients with resistant epilepsy

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Abstract

Objective: This study aims to evaluate the effects of C-reactive protein (CRP), albümin, mean platelet volume (MPV) values and neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLO), MPV/PLT ratio, CRP / Albumin ratios on seizure type and seizure control in epilepsy patients who are refractory or non-refractory to treatments. *Methods:* The study comprised 43 refractory epilepsy, 64 well-controlled epilepsy patients and control group including 68 healthy individuals. Mean platelet volume (MPV), platelet, CRP, and albumin values of the patients were studied. CRP / albumin ratio (CAR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLO), and the MPV/PLT ratio were determined. *Results:* The mean serum CRP and CAO were found to be significantly higher in refractory epilepsy patients compared to well-controlled epilepsy patients and healthy control groups, while MPV and albumin levels were found to be significantly lower.
Conclusions: Serum CRP and CAO were found to be significantly higher in refractory epilepsy patients compared to well-controlled epilepsy patients and healthy control groups, while MPV and albumin levels were found to be significantly lower. In addition, this inflammatory activity increases as the frequency of seizures increases and the duration of the disease increases. These findings suggest that increased inflammatory response may affect the patient's prognosis. In light of these findings, we think new treatment strategies that control the inflammatory response are necessary for patients with refractory epilepsy.

Keywords: Neuroinflamation, CRP, albumin, CRP / albumin ratio, Refractory epilepsy.

INTRODUCTION

Epilepsy is a neurological disease which influences nearly 65 million people worldwide.[1] Neuroinflammation is a response of the central nervous system (CNS) to tissue damage, infection, autoimmunity, seizure and stress conditions.[2] Although neuroinflammation is a normal response, it becomes a condition which leads to cellular dysfunction when it is prolonged and severe in the phenomena such as pain, stress, neurodegeneration and epilepsy.[3] Increasing evidence shows that neuroinflammation plays an important role in the etiology of various neurological diseases such as epilepsy, Alzheimer's disease and Parkinson's disease.[4] C-reactive protein (CRP) is a positive acute phase protein and increases as a response to inflammation whereas albumin is a negative acute phase protein and increases as a response to inflammation. The relationship between higher CRP levels and epilepsy has been emphasized in a study which analyzed the post-seizure serial serum CRP concentrations in patients with resistant focal epilepsy compared with healthy controls.[5] The previous studies have represented that hypoalbuminemia predicts poor outcomes depending on dose in several diseases such as status epilepticus (SE) and ischemic stroke and that it served as a prognostic marker of clinical course.[6,7] In the light of previous studies, CRP/albumin ratio (CAR) which combined negative and positive acute phase reactant proteins has been considered to be valuable as a prognostic marker in the diseases such as sepsis and hepatocellular carcinoma.[8,9] Increased CAR has been associated with poor prognosis in also Guillain–Barré syndrome (GBS) and subarachnoid hemorrhage.[10,11] Although the relationship between epilepsy and inflammation is well-documented, we have encountered no study that evaluated

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CAR in epilepsy patients in our literature review.

It has been manifested that systemic inflammation may trigger epileptic activity by impairing the function of the blood-brain barrier. The role of neutrophils in systemic inflammation is known, and it has been denoted that novel inflammatory parameters such as neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) play a role in the activity and prognosis of the diseases such as GBS, intracerebral hemorrhage and acute ischemic stroke.[12-14] In the limited number of studies which investigated the relationship between epilepsy and NLR, increased NLR was detected in the acute stages of convulsive SE and generalized seizures and these seizures have been reported to be associated with neutrophil-mediated inflammation.[15,16]

Mean platelet volume (MPV) and platelet count are the two main parameters used to evaluate platelet activation.[17] High MPV indicates larger and more reactive platelets resulting from increased platelet cycle and it can be used as a marker of the platelet activation and inflammation severity.[18] Many studies have revealed that there is an inverse relationship between MPV and platelet count.[19,20] It has been exhibited in the studies that MPV value is very high in pediatric patients with febrile convulsion (FC) compared with febrile children without convulsion whereas platelet count is low.[21,22]

In our study, we aimed to evaluate the impact of CRP, albumin and NLR, PLR, MPV/PLT, and CRP/Albumin values on seizure type and seizure control.

METHODS

The present study was carried out in the Department of Neurology, Harran University Medical Faculty Hospital. The study was approved by the local ethics committee (HRU/22.10.25) and carried out in accordance with Helsinki Declaration.

The population of the retrospectively planned study consisted of epilepsy patients who applied to the Harran University Medical Faculty Hospital Neurology Department between 01.01.2016 and 01.01.2022. All patients who applied to the outpatient clinic on the relevant date were included in the study, but patients who did not meet the criteria were excluded from the study. Patients over the age of 18 years, those with a diagnosis of epilepsy for at least 6 months, and those who did not have epileptic seizures in the last 72 hours were included in the study. The exclusion criteria are chronic systemic diseases, comorbid neoplasia, infectious or inflammatory diseases, hepatic or renal failure, coronary artery disease or ischemic heart disease, having a trauma, surgery or receiving immunomodulatory treatment in the recent time and presence of a central nervous system lesion (DNETs, hippocampal sclerosis, tuberous sclerosis, AVMs, malignant tumor.) in cranial magnetic resonance imaging (MRI). Forty three resistant epilepsy patients, 64 well-controlled epilepsy patients and 68 healthy individuals who met the criteria were included in the study.

The well-controlled epilepsy group included patients who had no seizures in the recent one year. The resistant epilepsy group was composed of patients in whom seizure control could not be achieved despite concurrent administration of two tolerable antiepileptic drugs (AEDs) (or separately) with appropriate doses and duration.[23] Healthy control group involved individuals with normal physical and neurological examination, similar age and gender, and no history of drug use.

Demographic data, age at disease onset, seizure type, seizure frequency, disease etiology, family history, number and type of the administered drug, electroencephalography (EEG) and cranial MRI findings of the patients were retrospectively screened from patient files in the hospital records and recorded.

Epilepsy patients were categorized into monotherapy and polytherapy groups according to the number of administered drugs, focal and generalized epilepsy according to seizure type, and resistant or controlled epilepsy according to seizure control status.

Neutrophil, lymphocyte, leukocyte, hemoglobin, hematocrit, reticulocyte distribution width (RDW), mean corpuscular volume (MCV), MPV, platelet, CRP and albumin values of the patients were obtained. CAR was calculated by dividing CRP by albumin level; NLR was calculated by dividing neutrophil count to lymphocyte count; PLR was calculated by dividing platelet count to lymphocyte count and MPV/PLT ratio was calculated by dividing MPV to platelet count.

Statistical analysis

Statistical analysis was performed using SPSS for Windows Versiyon 20.0 (Statistical Package for the Social Sciences) software. After the documentation of patient data, the distribution of study data was analyzed using Kolmogorov–Smirnov and Shapiro–Wilk normality tests.

Mann-Whitney U test was used for non-normally distributed variables. The comparison of normally-distributed variables between triple and two groups was performed using the One-way ANOVA Tukey test and Independent Sample T-test, respectively. ROC analysis was carried out to determine the diagnostic value of the variables. The frequency analysis of the variables was conducted using cross-tabulation and frequency tests. The statistical significance level was accepted as $p<0.05$ value in all tests.

RESULTS

The study included 107 epilepsy patients (mean age 31.03±10.20 years) and 68 healthy volunteers (mean age 32.83±11.00 years). The epilepsy patient group was composed of 43 (40.2%) patients with treatment-resistant epilepsy and 64 (59.8%) patients with well-controlled epilepsy. No significant difference was present between epilepsy patients and the healthy control group in terms of age and gender. The clinical findings of healthy controls and epilepsy patient groups were presented in Table 1.

Mean serum CRP levels and CRP/Albumin ratio values of the epilepsy patients were significantly higher than healthy controls (p=0.000, p=0.001, respectively). Albumin and MPV levels were significantly lower (p=0.025, p=0.036, respectively) (Table 2).

Compared with well-controlled epilepsy, resistant patients had significantly higher CRP levels and CRP/Albumin ratio values (p=0.026, p=0.037, respectively), and significantly lower albumin and MPV levels (p=0.018, p=0.044, respectively). The healthy control group had significantly higher CRP levels (p<0.001, p=0.025, respectively) and CRP/Albumin ratio values (p=0.005, p=0.06, respectively) compared with resistant and well-controlled epilepsy patients.

The comparison of resistant and well-controlled epilepsy groups with the healthy control group revealed that serum albumin and MPV levels were significantly lower in the resistant epilepsy group (p=0.003, p=0.007, respectively) and lower in the well-controlled epilepsy group, but not significantly (p=0.353, p=0.348, respectively) (Table 3). There was no statistically significant difference between the groups in terms of other biochemical parameters.

The seizure frequency of the epilepsy patients was found to be positively correlated with CRP and CAR (r=0.300, p=0.002; r=0.329, p=0.001, respectively) and negatively correlated with albumin level (r= -0.026, p=0.007). (Figure 1)

The disease duration of epilepsy patients

Table 1: Demographic and clinical parameters of epilepsy patient and control groups

	Patient group (n=107)	Control group (n=68)	P
Age, years	31.03±10.20	32.83±11.00	0.280
Gender, n (%)			0.069
Male	56 (52.3)	26 (38.2)	
Female	51 (47.7)	42 (61.8)	
Disease duration (years)	12.28±9.42		
Age of onset of disease	18.66±10.21		
Epileptic seizure frequency (per months)	2.46±3.01		
Seizure type, n (%)			
Focal	43 (40.2)		
Generalized	64 (59.8)		
Treatment, n (%)			
Monotherapy	60 (56.1)		
Polytherapy	47 (43.9)		
Response to treatment, n (%)			
Controlled	64 (59.8)		
Resistant	43 (40.2)		
Presence of family history, n (%)			
Yes	16 (15)		
No	91 (85)		

Table 2: Comparison of laboratory findings among the patient group with control groups

	Patient Group (n=107)	Control Group (n=68)	P
Leukocyte (10e3/uL)	2.33±0.71	2.24±0.50	0.322
Neutrophil (10e3/uL)	4.03±1.48	4.06±1.12	0.861
RBC (10e3/uL)	4.98±0.56	4.78±0.62	0.102
HTC (%)	43.51±4.38	44.72±5.44	0.125
HGB (g/dL)	15.39±12.17	14.15±1.66	0.302
MCV (fL)	87.68±6.86	89.28±6.24	0.199
MPV (fL)	8.06±1.42	8,56±1.56	**0.036**
PLT (10e3/uL)	251.82±56.69	265.52±56.80	0.122
RDW (%)	12.19±1.38	12.14±1.02	0.810
Albumin (g/dL)	4.43±0.38	4.56±0.37	**0.025**
CRP (mg/dL)	0.32±0.42	0.15±0.20	**<0.001**
NLR	1.81±0.69	1.92±0.84	0.381
PLR	116.27±40.13	123.81±36.01	0.199
MPV/PLT	0.03±0.01	0.03±0.01	0.437
CAR	0.07±0.09	0.036±0.05	**0.001**

Red blood cell: RBC, hematocrit: HTC, hemoglobin: HGB, mean corpuscular volume: MCV, mean platelet volume: MPV, platelet: PLT, red cell distribution width: RDW, C-reactive protein: CRP, neutrophil/lymphocyte ratio: NLR, platelet/lymphocyte ratio: PLR, CRP/Albumin ratio: CAR.

was found to be positively correlated with CRP and CAR (r=0.228, p=0.018; r=0.246, p=0.011, respectively) and negatively correlated with albumin level (r= -0.265, p=0.006). (Figure 2)

When the receiver operating characteristic analysis was applied for these four values, the cut-off value for CRP was 0.11 [AUC (area under the curve): 0.64, 95% CI: 0.56-0.72, sensitivity= 57.9%, specificity= 42.6%], cut-off value for albumin was 4.55 (AUC: 0.409, 95% CI: 0.320-0.497, sensitivity= 40.2%, specificity= 45.6%), and cut-off value for CAR was 0.27 (AUC: 0.646, 95% CI: 0.563-0.729, sensitivity= 57.9%, specificity= 58.8%). The size of the AUC was

Table 3. Serum albumin, CRP, CAR and MPV levels in groups

Group	Refractory	Well-controlled	Control	P
Albumin (g/dL)	4.32±0,44	4.51±0,31	4.56±0,37	& **0.018** * **0.003** # **0.353**
CRP (mg/dL)	0.43±0.55	0.25±0.28	0.15±0.20	& **0.026** * **<0.001** # **0.025**
CRP/Albumin Ratıo	0.10±0.13	0.05±0.06	0.03±0.05	& **0.037** * **0.005** # 0.06
MPV (fL)	7.73±1.51	8.28±1.33	8.56±1.56	& **0.044** * **0.007** # 0.348

& : Significance between refractory epilepsy and well-controlled epilepsy groups
*** :** Significance between refractory epilepsy and healthy control group
 # : Significance between healthy control group with well-controlled epilepsy
C-reactive protein: CRP, CRP/Albumin ratio: CAR, mean platelet volume: MPV.

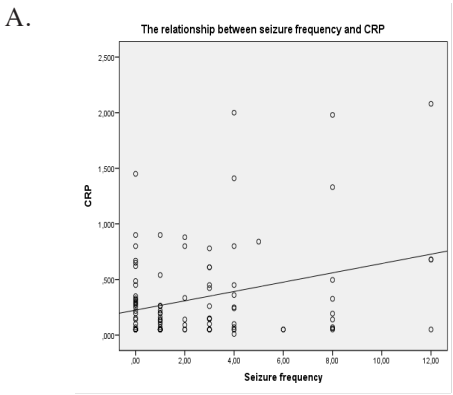

Figure 1. (A) The relationship between seizure frequency and CRP, (B) The relationship between seizure frequency and Albumin, (C) The relationship between seizure frequency and CAR.

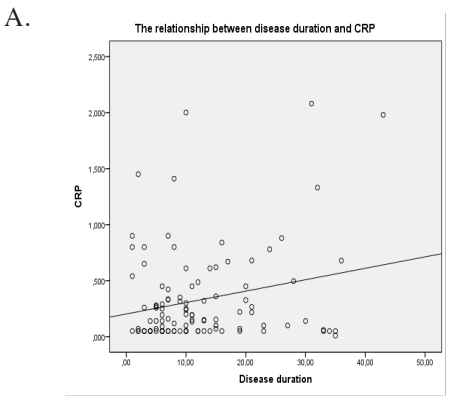

Figure 2. (A) The relationship between disease duration and CRP, (B) The relationship between disease duration and Albumin, (C) The relationship between disease duration and CAR.

insignificant as it contained a 95% CI of 0.50 found in the receiver operating characteristic analysis for MPV therefore no cut-off value was given for MPV. If given, the cut-off value would be 7.06 (sensitivity =78.5 %, specificity=77.9 %) (Figure 3).

DISCUSSION

In contrast to acute postictal changes, probable chronic interictal changes of inflammatory response in drug-resistant epilepsy patients have been rarely investigated and have not been well-defined. In our study, serum CRP and CAR levels of resistant epilepsy patients were significantly higher compared with well-controlled epilepsy patients and the healthy control group whereas MPV and albumin levels were found significantly lower.

Güneş *et al*. has determined that serum CRP levels of the patients with generalized epileptic

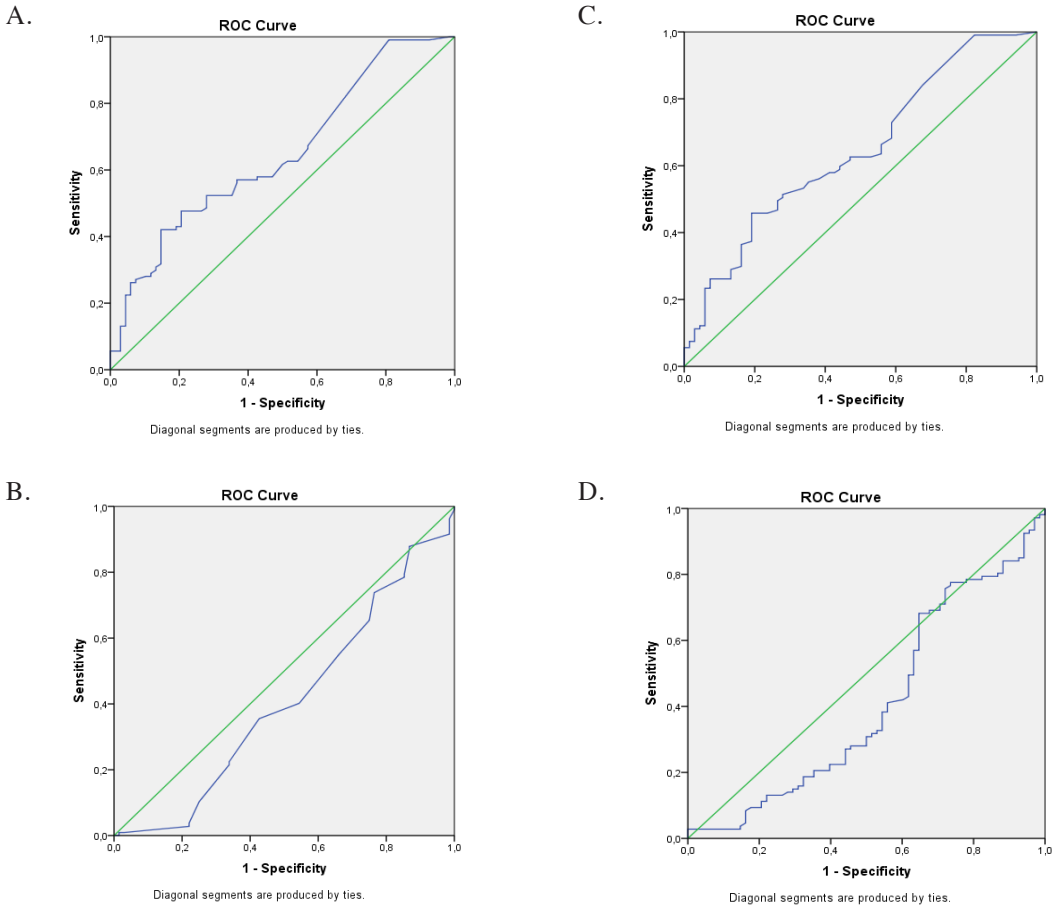

Figure 3. (A) Cut-off value for CRP=0.11 (AUC : 0.64, 95% CI: 0.56-0.72, sensitivity =57.9 %, specificity=42.6 %), (B) cut-off value for albumin= 4,55 (AUC: 0.409, 95% CI: 0.320-0.497, sensitivity =40,2%, specificity =45.6%) (C) cut-off value for CAR = 0,27 (AUC: 0.646, 95% CI: 0.563-0.729, sensitivity =57.9 %, specificity =58.8 %), (D) the AUC size is insignificant as the 95% CI found in the receiver processing characteristic analysis for the MPV is 0.50, and therefore, no cut-off value is given for an MPV. If given, the cut-off value would be 7,06 (sensitivity =78.5 %, specificity=77.9 %).
AUC, area under the curve; CRP, C reactive protein; CAR, C reactive protein/albumin ratio; MPV, Mean platelet volüme

seizures were higher in the acute stage and further higher in the subacute stage of the seizure compared with the control group, and they have attributed this condition to the delayed increase of acute phase protein CRP in blood.[15] In a study which investigated the post-seizure serial serum CRP concentrations of patients with resistant focal epilepsy, the relationship between higher serum CRP levels detected in the patients with epilepsy has been emphasized. They have also stated that secondary generalized tonic-clonic seizures exhibit a stronger inflammatory response than focal seizures.[5] A meta-analysis of 16 studies of 1,918 cases showed that epileptic patients had increased CRP levels compared to controls.[24]

In our study, the mean serum CRP level of the patients with resistant epilepsy was significantly higher than well-controlled epilepsy patients and the control group. Additionally, also well-controlled epilepsy patients had significantly higher mean serum CRP levels than the control group.

It has been manifested in a 5-year observational cohort study that the patient group with higher serum albumin levels in SE had a significantly lower probability of progression to refractory SE and death.[7] In this study, decreased serum albumin has been emphasized to be associated with systemic inflammation which sustained epileptic activity in SE patients.[7,19] It has been reported in another study that <35 g/L serum albumin at the onset of SE is an independent

predictor for refractory SE.[25] Özdemir *et al*. have ascertained that serum albumin decreased in the acute stage and increased in the subacute stage in children with convulsive SE, and this condition was explained with extravasation of albumin in the acute stage.[16] In our study, serum albumin levels of the epilepsy patients were significantly lower than the healthy control group consistent with the literature. Besides, serum albumin levels of resistant epilepsy patients were significantly lower than both well-controlled epilepsy patients and the healthy control group. Serum albumin levels of the patients with well-controlled epilepsy were detected to be lower than the healthy control group and the difference was not statistically significant.

CRP/albumin ratio is a novel combined inflammatory marker in the fields of oncology and neurology. Since CAR is a proportional value, it may be more consistent than individual blood parameters which may be affected by dehydration, excessive hydration and processing of blood samples.[26] It has been discovered that CAR is associated with severity and unfavorable outcomes of aneurysmal subarachnoid hemorrhage and is an independent determinant of ANCA-associated vasculitis mortality.[11,27] It has been additionally reported that CAR has higher predictivity for postoperative complications than CRP alone.[28] It has been presented in a study conducted on the patients in the intensive care unit that CAR is independently correlated with 30-day functional outcomes. The evidence has revealed that CAR reflected the disease severity more accurately than CRP or albumin and is a more reliable biomarker for the clinical monitoring of critical patients.[29] There is a limited number of studies which investigated the inflammatory parameters in resistant epilepsy patients, however, we have encountered no study which evaluated CAR in epilepsy patients. In our study, CAR values of resistant epilepsy patients were significantly higher than well-controlled epilepsy patients and the control group. Additionally, also well-controlled epilepsy patients were detected to have significantly higher CAR than the control group. In the study, seizure frequency and disease duration were found to be positively correlated with CRP and CAR, and negatively correlated with albumin level. These findings suggest that epileptic seizures continue on the basis of chronic inflammation and that inflammation is closely related to disease duration and seizure activation.

Mean platelet volume can be used as a marker of platelet activation and marker of inflammation severity.[18] Although Liu *et al*. has found that MPV was significantly higher in the simple FC group than the complex FC group in the differentiation of FC types (complicated FC or simple FC), literature data is conflicting on this subject.[30] For instance, Özaydın *et al*.[31] has shown that the MPV level of the simple FC group was higher than the complicated FC group whereas Göksugur *et al.*[32] and Yiğit *et al*.[33] has manifested that no significant difference was present between the two groups. In a study retrospectively conducted on children with FC in the recent time, MPV and platelet count were determined to be significantly lower in the pediatric patients with FC compared with non-convulsive febrile children and healthy control group, and it has been advocated that MPV is the most important protective factor associated with FC.[34] Compared with the healthy control group, serum MPV level was significantly lower in the resistant epilepsy group and lower in the well-controlled group, however, not statistically significant. This evidence suggests that lower MVP levels may be due to higher inflammation in epilepsy patients, particularly in the treatment-resistant epilepsy patient group, consistent with the studies in the literature which reported the relationship of serum MPV value with inflammation.

In recent studies, increased NLR was reported to be associated with neurodegenerative and cardiometabolic diseases.[35,36] Several recent studies have shown that high NLR is associated with poor prognosis and functional outcomes in patients with craniocervical artery dissection and acute ischemic stroke.[37,38] It has been determined in a retrospective study that serum NLR was higher than the control group in the blood samples of the patient with mesial temporal lobe epilepsy taken in the interictal stage, however, the difference was not statistically significant.[39] In another study, neutrophil count and NLR values were identified to be significantly higher in the acute stage of generalized epileptic seizures compared with the subacute stage.[23] This evidence has supported the hypothesis that epileptic seizures are associated with neutrophil-mediated systemic inflammation. In a recent systematic meta-analysis that included 7 studies from our country, they stated that NLR increased in epilepsy patients and could be a promising biomarker.[40]

In our study, no significant difference was encountered between resistant and well-controlled epilepsy groups in terms of NLR value in the interictal period. This finding can be explained by the fact that neutrophil plays a role in the early stages of inflammation.

This evidence shows that elevated inflammatory response may influence the prognosis of the disease. These easily accessible parameters may provide an opinion regarding the possibility of the progression of the disease to resistant epilepsy even in the early stage of the disease. The control of inflammation may be one of the methods to achieve seizure control in these patients.

The limitation of our study is its retrospective design. We concluded that carrying out prospective studies with larger patient groups to compare the values of the patients in the postictal early stage and interictal stage would be more valuable. Another limitation is that the study was classified by focal and generalized seizure types, but inflammatory parameters were not evaluated among these groups. We believe that these evaluations will contribute to the literature in future studies.

In conclusion, the resistant epilepsy patients were detected to have significantly higher serum CRP levels and CAR values and significantly lower MPV and albumin levels than the well-controlled patients and healthy control group. This condition is associated with increased inflammatory activity. In addition, this inflammatory activity increases as seizure frequency increases and disease duration prolongs. The interictal evaluation of serum CRP level and CAR which may be influenced by disease severity in the acute stage may provide an opinion about the inflammation which plays a role in the pathogenesis of epilepsy and they may be more consistent parameters to demonstrate the impact of chronic inflammation in seizure control. Our study represents that inflammatory markers including serum CRP, CAR, albumin and MPV levels can be used as lower-cost, more easily accessible and faster markers in predicting the prognosis of epilepsy disease. In light of these findings, novel treatment strategies to control the inflammatory response need further exploration in treatment-resistant epilepsy patients.

DISCLOSURE

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