

Hemogram parameters in epilepsy may be indicators of chronic inflammation and hypoxemia

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ABSTRACT

Objective: To evaluate the hemogram parameters of patients with epilepsy during and after periods of seizure, and to compare these parameters with those in healthy subjects.

Materials and method: Hemogram parameters of patients with epilepsy were analyzed retrospectively. Hemogram parameters were observed to display inflammatory status during seizure and seizure-free periods. Fifty-two patients with epilepsy and 48 healthy volunteers were included in the study.

Results: White blood cell (WBC), neutrophil, and lymphocyte levels were

significantly higher during seizures compared with seizure-free periods in patients with epilepsy. In addition, WBC, neutrophil and lymphocyte values of patients with epilepsy during seizure-free periods were significantly lower than those of healthy subjects. Independent of seizure status, patients with epilepsy had significantly increased mean corpuscular volume, mean platelet volume (MPV), and red blood cell distribution width (RDW) values compared with the controls.

Discussion: The increased MPV detected in patients with epilepsy in the present study was considered to be important because it reflects chronic inflammation. The neutrophil-lymphocyte ratio was not significantly different in patients with epilepsy compared with healthy individuals. Elevated RDW in patients with epilepsy is valuable because it is considered as the long-term memory of hypoxemia in this population.

Key Words: *Epilepsy, Hemogram parameters, Inflammation, MPV, RDW*

INTRODUCTION

Epilepsy is a disorder characterized by emerging and recurrent seizures with a wide variety of symptomatology and multifactorial causes. Physiologic studies have shown that seizures are caused by abnormal and synchronous hyperactivity of the neurons in the brain (1). Epilepsy affects 1-3% of the population worldwide (1,2). Epilepsy can also be described as episodic cerebral dysfunction due to increased excitability of nerve cells in the brain for different reasons. Epilepsy shows a stereotyped disorder of consciousness, behavior, feelings, and perceptions in a certain period of time, which are caused by increased rapid electrical discharges in gray matter (3). Although the etiology of epilepsy is unknown, underlying mechanisms have been pathophysiologically focused on cerebral vascular disease, trauma, and neoplasms (4-6). In this context, inflammatory conditions, clinical situations, and influencing factors related to these diseases may be associated with epilepsy. An inflammatory state and changes in blood parameters could be considered to persist into later periods of epilepsy. The role of inflammatory mechanisms in brain tissue has been the focus in epileptogenesis in recent studies (7,8). Data obtained from experimental models and human brain tissue suggest the role of inflammation in epilepsy (9). Chemokines are responsible for leukocyte uptake in epileptic brains as a consequence of neuroinflammation (10). Recent studies suggested a prognostic value and an association of the neutrophil (NEU)-lymphocyte ratio (NLR) in inflammatory conditions such as cardiovascular diseases, solid tumors, and smoking (11).

Chronic inflammation can promote hyperexcitation in the brain and may cause recurrent seizures. There are some biomarkers under speculation in this context. These markers have been proposed to be used to differentiate seizure types and develop alternative therapies. As information about the role of inflammation in disease progression increases, the use of disease-modifying therapy for the development of specific anti-inflammatory drugs and new treatment approaches will come on the agenda (12).

In a study in 2012, Özyaydin et al. proposed the Mean Platelet Volume (MPV) as a marker of differentiation of simple and complex febrile seizures (13). In a recent study, however, there was no difference between simple and complex febrile seizures (14).

There are few studies in the literature about hemogram parameters in patients with epilepsy. It could be considered that there would be changes in hemogram parameters in seizure periods in patients with epilepsy. In this study, we aimed to evaluate the hemogram parameters of patients with epilepsy during and after periods of seizure, and to compare these parameters with those in healthy subjects.

We hypothesized that hemogram parameters of patients with epilepsy during seizure were significantly different than those of non-seizure periods. We also hypothesized that hemogram parameters would be different in patients with epilepsy during seizure or seizure-free periods compared with those of healthy individuals.

METHODS

We retrospectively screened the files of subjects who were followed up for epilepsy in our clinic. We recorded the hemogram parameters of these patients during seizure and seizure-free periods. We also recorded the hemogram parameters of healthy individuals who visited our outpatient clinics for routine tests. The study group consisted of subjects aged over 18 years with generalized tonic clonic seizure with normal C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) values. Healthy volunteers with normal infection parameters (CRP) sedimentation, leukocyte count) were included as control group. Volunteers with infection, rheumatologic disease, Familial Mediterranean Fever (FMF), obesity, and metabolic diseases were excluded from the study.

The dependent variables of the study were hemogram parameters (WBC, hematocrit, NEUs, lymphocytes, platelets, MPV, Red blood cell Distribution Width (RDW), Platelet Distribution Width (PDW), NLR, and the independent variables were having seizures and post seizure period. During the planning of this study, approval of local Medical Ethics Committee was obtained (reference number: 2015/12).

The SPSS software was used for to conduct the statistical analyses. Numbers and percentages are used for descriptive statistics and for categorical variables and presented as mean, standard deviation, median, 25th percentile, 75th percentile, and minimum and maximum. The Mann-Whiney U test was

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used for the comparison of nonhomogeneous parameters and the t-test was used for homogenous variables. Dependent two-group comparisons were performed using the Wilcoxon signed-rank test if non-homogenous distribution was considered, and the paired t-test was used for homogenously distributed parameters. The Chi-square test was used for categorical variables. The level of statistical significance was set at p values lower than 0.05.

RESULTS

A total of 32 female (61.5%) and 20 (38.5%) male with epilepsy were included in the study group. As a control group, 30 (61.2%) female and 19 (38.8%) male healthy volunteers were included. The mean ages of the men in study and control groups were 31.30 ± 7.05 years and 35.26 ± 6.85, respectively. The mean ages of the women in study and control groups were 31.75 ± 9.94 and 32.46 ± 7.22 years, respectively. There was no difference between the groups in terms of sex and age (Tables 1 and 2) (both p>0.05).

TABLE 1
Comparison of sex between the groups

	Study group		Control Group		Total	
	n	%	n	%	n	%
Sex						
Female	32	61.5	30	61.2	62	61.4
Male	20	38.5	19	38.8	39	38.6
Total	52	100	49	100	101	100
Pearson Chi-square	P=0.974					

TABLE 2
Age of the groups

Sex	Group	Mean ± SD	Total(n)
Male	study	31.30 ± 7.05	20
	control	35.26 ± 6.85	19
Female	study	31.75 ± 9.94	32
	control	32.46 ± 7.22	30

MCV, RDW, and MPV were significantly elevated in patients with epilepsy compared with the controls (all p<0.05). Table 3 shows the comparison of hemogram parameters between the groups.

TABLE 3
Comparison of hemogram parameters between the epilepsy group and control group during seizure

T test	Study group *(n=52)	Control group *(n=49)	p
	mean ± SD		
HGB	14.04 ± 1.48	13.97 ± 1.70	0.802
HTC	41.50 ± 3.90	41.50 ± 4.36	0.999
MCV	87.60 ± 4.64	85.66 ± 4.81	0.042
RDW	14.70 ± 1.66	13.74 ± 1.55	0.003
PLT	235.59 ± 73.99	247.35 ± 47.52	0.342
MPV	9.15 ± 1.32	8.05 ± 1.41	0.001
Mann-Whitney U median (min-max)			
WBC	7.6 (3.28-16.4)	7.0 (5.0-11.1)	0.348
NEU	4.17 ± 1.57-12.14	4.3 ± 2.40-7.71	0.615
Lymphocyte	1.98 ± 0.22-8.60	2.20 ± 1.30-3.60	0.905
NLR	1.84 ± 0.41-12.33	1.89 ± 0.75-4.59	0.959
PDW	16.50 ± 12.00-21.60	16.00 ± 13.00-20.40	0.391

HGB: hemoglobin, HTC: hematocrit, MCV: mean corpuscular volume, RDW:red blood cell distribution width, PLT: platelet MPV:mean platelet volume, WBC: White blood cell, NEU: neutrophil, NLR: neutrophil/lymphocyte ratio, PDW: platelet distribution width.

WBC, NEU, MCV, RDW, MPV, lymphocyte, and PDW values were significantly different in the seizure-free period of the epilepsy group compared with the controls (all p<0.05). WBC, NEU, and lymphocytes were significantly higher in the controls compared with the epilepsy group (Table 4).

TABLE 4
Comparison of hemogram parameters between the epilepsy group and control group during the seizure-free period

T test	Studygroup *(n=52)	Controlgroup *(n=49)	p
	mean ± SD		
WBC	6.17 ± 1.40	7.15 ± 1.51	0.001
NEU	3.50 ± 0.95	4.35 ± 1.39	0.001
HGB	13.86 ± 1.40	13.97 ± 1.70	0.748
HTC	41.21 ± 3.94	41.50 ± 4.36	0.727
MCV	88.14 ± 5.61	85.66 ± 4.81	0.02
RDW	14.58 ± 1.72	13.74 ± 1.55	0.011
PLT	226.30 ± 64.37	247.35 ± 47.52	0.064
MPV	8.92 ± 1.55	8.04 ± 1.41	0.004
Lymphocyte	2.04 ± 0.68	2.30 ± 0.60	0.045
Mann-Whitney U median (min-max)			
NLR	1.69 (0.71-6.13)	1.87 (0.75-4.59)	0.28
PDW	16.6 (11.9-21)	16 (13-20.4)	0.04

HGB: hemoglobin, HTC: hematocrit, MCV: mean corpuscular volume, RDW:red blood cell distribution width, PLT: platelet MPV:mean platelet volume, WBC: White blood cell, NEU: neutrophil, NLR: neutrophil/lymphocyte ratio, PDW: platelet distribution width.

WBC, NEU, and lymphocyte values were significantly higher in patients with epilepsy during seizure compared with those of the seizure free period (p<0.05) (Table 5).

TABLE 5
Comparison of hemogram parameters in the epilepsy group during seizure and seizure-free periods

Paired Sample Test	Epilepsy group (seizure)	Epilepsy group (seizure-free period)	p
	Mean ± SD		
HGB	14.01 ± 1.58	13.91 ± 1.55	0.158
HTC	41.50 ± 4.11	41.35 ± 4.14	0.419
MCV	86.66 ± 4.80	86.94 ± 5.36	0.252
RDW	14.23 ± 1.67	14.17 ± 1.68	0.646
PLT	241.74 ± 62.53	236.52 ± 57.52	0.194
MPV	8.61 ± 1.46	8.50 ± 1.54	0.19
Wilcoxon signed-rank test	Median (Min-Max)		
WBC	7.60 ± 3.28-16.40	6.00 ± 3.85-12.10	0.001
NEU	4.17 ± 1.57-12.14	3.38 ± 1.97-6.40	0.001
PDW	16.50 ± 12-21.6	16.60 ± 11.9-21	0.39
Lymphocyte	1.98 ± 0.22-8.6	1.94 ± 0.66-4.5	0.041
NLR	1.84 ± 0.41-12.33	1.68 ± 0.71-6.13	0.145

DISCUSSION

WBC, NEU, and lymphocyte counts were significantly higher in patients with epilepsy during seizure and WBC, NEU, and lymphocyte values were significantly lower in the seizure-free period compared with controls (p<0.05). Regardless of seizure, MPV, RDW, and MCV values were higher in the epilepsy group compared with the control group.

Some studies reported changes in WBC or lymphocyte levels in patients with epilepsy during seizure or seizure-free periods. Moreover, elevation in prolactin and WBC levels have been proposed to be related with seizure periods and even with the duration of the seizures (15-17). Consistent with the literature, in our study, elevated WBC, NEU, and lymphocytes were determined in the seizure period in patients with epilepsy, whose CRP levels ruled out infection.

In line with a recent study (18) in the present study, NLR was not significantly different between patients with epilepsy and controls. Both NEUs and lymphocytes showed a global increase. Unlike studies that reported a cytokine release that could be associated with an increase in NLR (19) we observed no cytokine release that might increase NLR nor a huge increase in NEUs that might suppress lymphocyte levels. This difference may be a consequence of recurrent seizures in complex febrile seizures and fever or infection, which might accompany febrile convulsions. Patients in status epilepticus may also be useful in future studies to investigate whether an increase exists in this direction. Studying the elevation of NLR in patients in status epilepticus could add much to the literature.

Recent studies focused on inflammation in brain tissue (7,20). Some reports speculated that antiinflammatory medicine used during acute infections might prevent epileptogenesis. Moreover, blockade of proinflammatory interleukins may cease seizures in patients with status epilepticus (21,22).

MPV elevation without a significant change in the number of platelets could reflect the ongoing inflammatory condition in patients with epilepsy. Increased MPV is supposed to be a marker of platelet activation, and larger platelets can be prothrombotic and may aggregate more easily. Indeed, MPV elevation is considered as the precursor of inflammation or an atherosclerotic event in many acute and chronic inflammatory and vascular diseases (23-26). Elevated MPV was introduced as an inflammation marker in inflammatory conditions and it was suggested to be correlated with poor prognosis independent of other clinical events in acute cerebrovascular diseases (24). To our knowledge, this is the first study to report elevated MPV in generalized epilepsy. A number of studies were conducted to observe the role of inflammation in the development of epilepsy and epileptic seizures. Ozaydin et al. proposed MPV as a marker to differentiate simple and complex febrile seizures (13). However, a more recent study found no MPV elevation (19). The MPV increase in the seizure and seizure-free periods of our patients cannot be fully explained by the reports in the literature. However, epilepsy is a dynamic process, and inflammation could supply continuity in seizure-free periods despite it being more pronounced during attacks. The MPV increase might be an extension of an inflammatory process that continues at a low level (27). MPV elevation is also likely to be associated with inflammation in our case. It would be useful to investigate the correlation of MPV elevation with other inflammatory cytokines.

RDW is a hematologic parameter that reflects the size variability of erythrocytes. Recent studies emphasized its importance in the prognosis and mortality of many diseases. In a recent study, RDW was shown to be ineffective at distinguishing simple and complex febrile seizures (18). However, RDW elevation was proposed to be used as a biomarker for diseases associated with acute hypoxemia, and it is capable of long-term memory of serious illness causing hypoxia (25,28). Hypoxia is known to occur in patients with epilepsy during seizures and it is responsible for brain damage. RDW elevation in patients with epilepsy may be associated with short-term hypoxemia. The hematocrit and hemoglobin levels in the study group were not different compared with the control group. Therefore, this increase in RDW was not associated with anemia, especially iron deficiency anemia, because epilepsy could be related with inflammation, and because RDW increases in inflammatory conditions (29,30). It is not surprising that we found more elevated RDW in the study group than in the healthy controls. We did not study the correlation of hemogram parameters and frequency of seizures. Therefore, this elevation in RDW could not be related with seizures in patients with epilepsy.

Although the hemoglobin and hematocrits were not different between the study and control groups, MCV was significantly elevated in the study group compared with the controls. Antiepileptic drugs may interact with folate and vitamin B12 metabolism, which results in megaloblastic anemia (31). Our patients were on treatment with either valproic acid, diphenylhydantoin, levetiracetam, topiramate or lamotrigine. However, we did not study B12 and folate levels in the present study. On the other hand, the MCV of the subjects in the present study were in the normal range, even the elevated MCV in the study group.

In conclusion, the present study adds to the literature about the association between epilepsy and changes in hematologic parameters. Elevated WBC, MPV, and RDW values may be a consequence of ongoing inflammatory processes in epilepsy pathogenesis. In addition, RDW is an important parameter in terms of chronic hypoxia in epilepsy.

REFERENCES

1. Shneker BF, Fountain NB. *Epilepsy. Dm Disease-a-Month.* 2003;49(7):426-78.
2. Manford M. The National General-Practice Study of Epilepsy - the Syndromic Classification of the International-League-against-Epilepsy Applied to Epilepsy in a General-Population. *Arch Neurol.* 1992;49(8):801-8.
3. Marchi N, Granata T, Janigro D. Inflammatory pathways of seizure disorders. *Trends Neurosci.* 2014;37(2):55-65.
4. Luhdorf K, Jensen LK, Plesner AM. Etiology of Seizures in the Elderly. *Epilepsia.* 1986;27(4):458-63.
5. Lossius MI. Incidence and predictors for post-stroke epilepsy. A prospective controlled trial. The Akershus stroke study. *Eur J Neurol.* 2002;9(4):365-8.
6. Hesdorffer DC, V.C. Risk factors, in *Epilepsy: A comprehensive*, J.A.T.P. Engel, Editor. Lippincott-Raven Publishers: Philadelphia. 1997;59-67.
7. Vezzani A. Epilepsy and Inflammation in the Brain: Overview and Pathophysiology. *Epilepsy Currents.* 2014;14:3-7.
8. Cerri C, Caleo M, Bozzi Y. Chemokines as new inflammatory players in the pathogenesis of epilepsy. *Epilepsy Res.* 2017;136:77-83.
9. Aronica E. Neuroinflammatory targets and treatments for epilepsy validated in experimental models. *Epilepsia.* 2017;58(S3):27-38.
10. Varvel NH. Infiltrating monocytes promote brain inflammation and exacerbate neuronal damage after status epilepticus. *Proc Natl Acad Sci.* 2016;113(38):E5665-74.
11. Azab B, Camacho-Rivera M, Taioli E. Average Values and Racial Differences of Neutrophil Lymphocyte Ratio among a Nationally Representative Sample of United States Subjects. *Plos One.* 2014;9(11).
12. Amhaoul H. Brain inflammation in a chronic epilepsy model: Evolving pattern of the translocator protein during epileptogenesis. *Neurobiol Dis.* 2015;82:526-39.
13. Ozaydin E. Differences in iron deficiency anemia and mean platelet volume between children with simple and complex febrile seizures. *Seizure Eur J Epilep.* 2012;21(3):211-4.
14. Nikkhah A, Salehionran MR, Asefi SS. Differences in Mean Platelet Volume and Platelet count between children with simple and complex febrile seizures. *Iran J Child Neurol.* 2017;11(2):44.
15. Sundararajan T, Tesar GE, Jimenez XF. Biomarkers in the diagnosis and study of psychogenic nonepileptic seizures: A systematic review. *Seizure.* 2016;35:11-22.
16. Luef G. Hormonal alterations following seizures. *Epilepsy Behav.* 2010;19(2):131-3.
17. Shah AK. Peripheral WBC count and serum prolactin level in various seizure types and nonepileptic events. *Epilepsia.* 2001;42(11):1472-5.
18. Yigit Y. The role of neutrophil-lymphocyte ratio and red blood cell distribution width in the classification of febrile seizures. *Eur Rev Med Pharmacol Sci.* 2017;21:554-9.
19. Goksugur S. Neutrophil-to-lymphocyte ratio and red blood cell distribution width is a practical predictor for differentiation of febrile seizure types. *Eur Rev Med Pharmacol Sci.* 2014;18(22):3380-5.
20. Van Vliet EA. Neuroinflammatory pathways as treatment targets and biomarker candidates in epilepsy: emerging evidence from preclinical and clinical studies. *Neuropathol Appl Neurobiol.* 2017.
21. Fabene PF. A role for leukocyte-endothelial adhesion mechanisms in epilepsy. *Nat Med.* 2008;14(12):1377-83.
22. Uludag IF. IL-1beta, IL-6 and IL1Ra levels in temporal lobe epilepsy. *Seizure.* 2015;26:22-5.

23. Soydinc S. Mean Platelet Volume Seems To Be a Valuable Marker in Patients with Systemic Sclerosis. *Inflammation*. 2014;37(1):100-6.
24. Greisenegger S. Is elevated mean platelet volume associated with a worse outcome in patients with acute ischemic cerebrovascular events? *Stroke*. 2004;35(7):1688-91.
25. Endler G. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. *Br J Haematol*. 2002;117(2):399-404.
26. Kisacik B. Mean Platelet Volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. *Joint Bone Spine*. 2008;75(3):291-4.
27. Kapsoritakis AN. Mean platelet volume: a useful marker of inflammatory bowel disease activity. *Am J Gastroenterol*. 2001;96(3):776-81.
28. Ycas JW, Horrow JC, Horne BD. Persistent increase in red cell size distribution width after acute diseases: A biomarker of hypoxemia? *Clinica Chimica Acta*. 2015;448:107-17.
29. Aktas G. Could Red Cell Distribution Width be a Marker in Hashimoto's Thyroiditis? *Exp Clin Endocrinol Diabetes*. 2014;122(10):572-4.
30. Brusco G, Di Stefano M, Corazza GR. Increased red cell distribution width and coeliac disease. *Dig Liver Dis*. 2000;32(2):128-30.
31. Verrotti A. Anticonvulsant drugs and hematological disease. *Neurol Sci*. 2014;35(7):983-93.