Research article

The utility of hematological indices in differentiation between general and focal onset epilepsy

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ABSTRACT

Introduction and Aim: Epilepsy is one of the most common neurological disorders with mainly focal and generalized onset types. Discrimination between these types is of paramount importance because the prescription of antiepileptic drugs (AEDs) depends on such decimation. Currently this made mainly upon the medical history of the patient. The aim of the study is to evaluate the role of hematological indices in discrimination between focal and generalize onset epilepsy.

Patients and Methods: This cross-sectional study included a total of 100 patients with epilepsy (mean age 21.44±10.5, range 6-52, 67 males and 33 females). Blood samples were collected for the participant and complete blood count (CBC) was performed. Furthermore, serum concentration of K+ and Na+ was determined.

Results: There were 38 patients with generalized and 62 patients with focal onset epilepsy. In multivariate initial analysis, each of mean platelet volume (MPV) (odds ratio (OR)= 2.56, 95%CI=1.09-13.22, p= 0.046) and serum Na+ (OR= 3.85, 95%CI=1.13-13.19, p= 0.032) were significantly associated with generalized onset epilepsy. Furthermore, two AEDs: carbamazepine and valproic acid were also independently associated with generalized and local onset epilepsy, respectively.

Conclusion: These data indicate the possible utility of MPV in the discrimination between generalized and focal onset epilepsy. However, further studies are required for more reliable conclusions.

Keywords: Focal and generalized onset epilepsy; mean platelet volume; hematological indices; receiver operating characteristic curve.

INTRODUCTION

Epilepsy is a disorder that causes recurring seizures, requires typically two unprovoked seizures, separated by greater than 24 hours (1).Various brain diseases are risk factors or causes of epilepsy (2). Epilepsy can also be described as episodic cerebral dysfunction due to increased excitability of nerve cells in the brain for different reasons (3). Physiological studies have shown that seizures are caused by abnormal and synchronous hyperactivity of the neurons in the brain (4). Seizure onset can be focal (seizures arising in one hemisphere of the brain), generalized (seizures originating in both hemispheres simultaneously), and unknown (5,6).

EEG plays a serious diagnostic role by sampling of electrical brain activity (7). Epileptiform discharges in EEG are greatly associated with epilepsy, but pathognomonic. Validation of seizures can be made only when a seizure is captured during an EEG. Furthermore, in-comparison to sensitivity and specificity of EEG for epilepsy which are 50% and 98-99%, respectively, serial EEGs can rise the sensitivity up to 80-90% (6).

Most febrile seizures occur outside of hospitals, and information on such seizures is usually obtained from their parents. Currently, there are no objective parameters to distinguish the focal and generalized types of seizures. Therefore, objective diagnostic indicators to determine the type of seizures in non-hospital seizures are needed (8).

Goksugur *et al.*, suggested that Neutrophil-Lymphocyte Ratio (NLR) and Red Cell Distribution width (RDW) may be used to objectively make this distinction (9), taking into consideration that NLR is an inexpensive, easily accessible, and easily calculable parameter that has been used for evaluation of systemic inflammation. Moreover, in a study in 2012, Özaydın *et al.*, suggested that the Mean Platelet Volume (MPV) may be practice as a marker to differentiate between simple and complex febrile seizures (10).

There are very few studies in the literatures which have addressed the role of different hematological

parameters in differentiation between different types of epilepsy. It could be considered that there would be changes in these parameters even in seizure free periods. In this study, we aimed to evaluate the hematological parameters of patients with generalized onset epilepsy and to compare these parameters with those with focal onset epilepsy.

MATERIALS AND METHODS

This is a prospective cross-sectional study including 100 patients with epilepsy who were attending the outpatient clinic of the Neuroscience Centre/ Baghdad from January 2020 through June 2020. All patients were reviewed and examined by a neurology consultant before being considered eligible for the study. The study was approved by the Institute Review Board (the local Ethical Committee of the College of Medicine, Al-Nahrain University). A written consent from each participant was obtained prior to sample collection after explaining the aim of study. Each patient was given the complete unconditioned choice to withdraw anytime. The confidentiality of data throughout the study was guaranteed and the patients were assured that data would be used for research purpose only.

Patients with recent infection including COVID-19, those experienced seizures on the day of presentation, patients with autoimmune disease or on immuno-modulating drugs such as steroids or chemotherapeutic agents, history of blood infusion or PLTs; use of anticoagulant drugs prior to admission; and chemotherapy, radiotherapy or bone marrow transplantation one month before admission, and patients with a history of recent head trauma were excluded from the study.

Eligible patients were underwent physical examination. The collected data included patients' demographics (age, gender), type of epilepsy according to classification of the International League Against Epilepsy (ILAE) generalized and focal (5), epilepsy treatment.

Sample collection and laboratory investigations

Three mL of peripheral blood were collected from each participant. Hematology auto analyzer (Huroba ABX/India) was used to measure blood parameters. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte. Furthermore, serum Na+ and K+ was measured using Electrometer (Compolyse-450/Japan).

Statistical analysis

All statistical analyses were performed using SPSS statistical software, version 24 (SPSS, IBM company, Chicago, USA). The normal distribution of distribution of continuous data was tested with Shapiro Wilk test.

Normally distributed quantitative variables are presented as mean ± SD and analyzed with independent t-test. Categorical variables are expressed as counts and percentages and analyzed with Chi-square. Receiver operating characteristic (ROC) curve analyses was used to evaluate the diagnostic value of MPV in differentiation between focal and generalized onset epilepsy. For all tests, a significant level of statistics was considered when $p<0.05$

RESULTS

Demographic and clinical characteristics of the patients

This study included 100 patients with a mean age of 21.44±10.5 years (range 6-52 years), of which two-thirds were males. In 38% of the patients, the epilepsy had generalized onset. Nine drugs were used for the treatment of epilepsy, the most common of which was levetiracetam used by 54% of the patients, followed by carbamazepine (44%) and clonazepam (17%). Oxcarbazepine, phenytoin and clonazepam were less commonly used accounting for 5%, 5% and 4% of the patients, respectively. In 47 (47%) of the patients, the EEG findings were abnormal (Table 1).

Association of demographic, clinical and biochemical parameters with the type of epilepsy

Each of patient's age, gender and serum potassium were comparable between patients with focal and generalized onset epilepsy with no significant difference. In contrast patients with generalized onset epilepsy demonstrated higher serum level of sodium than those for focal onset epilepsy (138±2.53 mmol/L vs. 136.41±3.54 mmol/L) with a significant difference. Tegretol (carbamazepine) was more frequently used by patients with focal than those with generalized onset epilepsy (62.9% vs. 13.16%) with a highly significant difference. The reverse was true for Depakin (valproic acid) (6.45% vs. 68.42%) with a highly significant difference (Table 2).

Association of hematological indices with the type of epilepsy

Most hematological indices were comparable between patients with generalized and focal onset epilepsy, with no significant differences. The mean ESR in generalized onset group was 10.13±9.95 mm/hr compared with 14.39±12.36 mm/hr in focal onset group; however, the difference being not significant (p=0.071). In contrast, mean RDWC was higher in generalized than focal onset group

(16.59±3.09% vs. 15.65±1.76) with marginally significantly difference (p=0.054). The only hematological index with a significant variation between the two groups was MPV. Mean MPV in patients with generalized onset epilepsy was 9.32±1.0 fl compared with 8.67±0.86 ft in patients with focal onset epilepsy with highly significant difference (Table 3).

Multivariate analysis

Variables which demonstrated a p-value of ≤ 0.1 in their association with the type of epilepsy were subjected to multivariate analysis wherein each quantitative variable was categorized into a binomial variable using appropriate cut of value. The result is shown in table 4. Two parameters were independently associated with generalized onset epilepsy. These were serum Na+ >137 mmol/L (OR= 3.85, 95%CI=1.13-13.19, p= 0.032) and MPV>9.0 fl (OR=2.56, 95% CI=1.09-13.22, p=0.046). Furthermore, carbamazepine and valproic acid were also independently associated with generalized and local onset epilepsy, respectively (Table 4).

In the context of discrimination between generalized and focal epilepsy, the MPV has an area under the curve of 0.679, 95%CI= 0.57-0.788, p= 0.003. The sensitivity and specificity of the test at MPV= 8.65 fl was 0.74 and 0.53, respectively (Figure 1).

Table 1: Demographic and clinical characteristics of the study population (n=100)

Variables	Value
Age, years	
Mean±SD	21.44±10.5
Range	6-52
Gender	
Male	67 (67%)
Female	33 (33%)
Types	
Generalized	38 (38%)
Focal	62 (62%)
Treatment of Epilepsy	
Keppra (Levetiracetam)	54 (54%)
Tegretol (Carbamazepine)	44 (44%)
Depakin (valproic acid)	40 (40%)
Rivotril (Clonazepam)	17 (17%)
Lomatrigin (Lamotrigine)	9 (9%)
Topamax (Topiramate)	6 (6%)
Trileptal (Oxcarbazepine)	5 (5%)
Phenytoin (Phenytoin)	5 (5%)
Clonazepam (Clonazepam)	4 (4%)
EEG findings	
Normal	53 (53%)
Abnormal	47 (47%)

SD: standard deviation, a patient using >one drug

Table 2: Association of demographic, and clinical features with the type of epilepsy

Variables	**Generalized (n=38)**	**Focal (n=62)**	**p-value**
Age, years	19.89 ± 9.82	23.9 ± 11.8	0.084
Gender			
Male	23 (60.52%)	44 (70.97%)	0.281
Female	15 (39.47%)	18 (29.03%)	
Potassium, mmol/L	4.16 ± 0.49	4.32 ± 0.51	0.201
Sodium, mmol/L	138 ± 2.53	136.41 ± 3.54	**0.046**
Treatment of Epilepsy			
Keppra	19 (50%)	35 (56.45%)	0.530
Tegretol	5 (13.16%)	39 (62.9%)	**<0.001**
Depakin	26 (68.42%)	4 (6.45%)	**<0.001**
Rivotril	10 (36.32%)	7 (11.29%)	0.052
Lomatrigin	2 (5.26%)	7 (11.29%)	0.476
Topamax	1 (2.63%)	5 (8.06%)	0.403
Trileptal	0	5 (8.06%)	0.153
Phenytoin	0	5 (8.06%)	0.153
Clonazepam	0	4 (6.45%)	0.294

Table 3: Association of hematological indices with the type of epilepsy

Variables	Generalized (n=38)	Focal (n=62)	p-value
Total WBC×10^3/ml	6.63 ± 1.56	7.54 ± 4.55	0.239
ESR (mm/hr)	10.13 ± 9.95	14.39 ± 12.36	0.071
NLR	2.44 ± 4.24	2.38 ± 2.52	0.530
PDWC, %	38.57 ± 4.25	38.13 ± 4.91	0.642
RDWC, %	16.59 ± 3.09	15.65 ± 1.76	0.056
PCT, %	0.22 ± 0.08	0.24 ± 0.06	0.271
MCHC, g/l	34.32 ± 1.61	34.84 ± 1.69	0.134
MCH, pg	27.74 ± 4.0	27.77 ± 2.97	0.959
Hb, g/dl	13.03 ± 2.03	13.05 ± 1.86	0.97
Monocyte×10^3/ml	0.35 ± 0.2	0.3 ± 0.22	0.273
HCT, %	37.89 ± 5.41	37.78 ± 5.34	0.92
MCV, fl	80.61 ± 9.66	80.19 ± 6.29	0.806
MPV, fl	9.32 ± 1.0	8.67 ± 0.86	**0.001**
PLT×10^3/ml	258.86 ± 86.12	270.96 ± 83.75	0.061
RBC×10^3/ml	4.71 ± 0.63	4.74 ± 0.62	0.787
Lymphocyte×10^3/ml	2.56 ± 0.8	2.25 ± 0.94	0.097

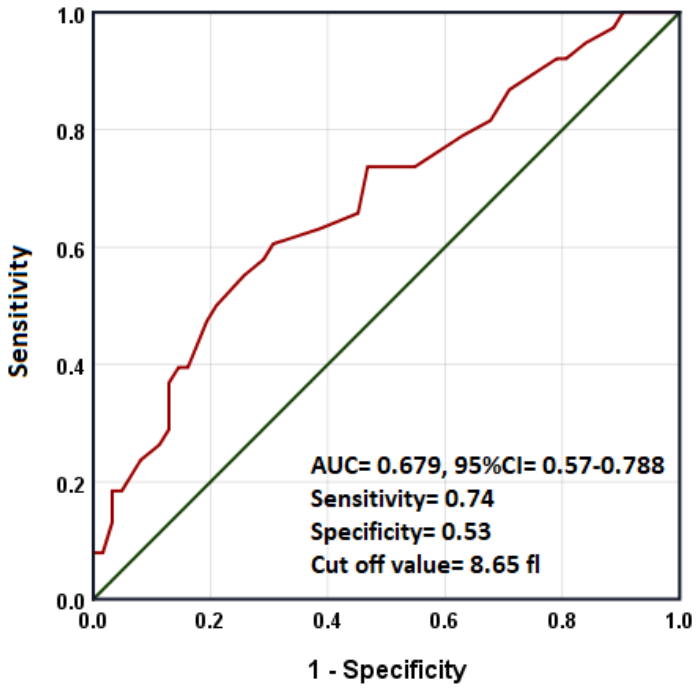

Fig. 1: Receiver operating characteristic curve for MPV in the context of discrimination between generalized and focal epilepsy.

Table 4: Multivariate analysis

Variables	Generalized (n=38)	Focal (n=62)	p-Value	OR(95%CI)
Age, years				
≤20	23(60.53%)	29(46.77%)	0.412	1.0
>20	15(39.47%)	33(53.23%)		1.59(0.52-4.87)
RDWE				
≤15	21(55.26%)	26(41.94%)	0.264	1.0
>15	17(44.74%)	36(58.06%)		1.95(0.59-6.32)
ESR, mm/hr				
≤10	28(73.68%)	33(53.23%)	0.314	1.0
>10	10(26.32)	29(46.77%)		0.54(0.17-1.78)
Lymphocyte×10^3/ml				
≤2.5	21(55.26%)	44(70.97%)	0.142	1.0
>2.5	17(44.74%)	18(29.03)		2.42(0.85-4.44)
Sodium				
≤137	20(52.63%)	46(74.19%)	**0.032**	**1.0**
>137	18(47.37%)	16(25.81%)		**3.85 (1.13-13.19)**
MPV				
≤9.0	16(42.11%)	44(70.97%)	**0.046**	**1.0**
>9.0	22(57.89%)	18(29.03%)		**2.56 (1.09-13.22)**
Platelets×10^3/ml				
≤250	20(52.63%)	32(51.61%)	0.116	1.0
>250	18(47.37%	30(48.39%)		1.71(0.84-5.44)
Depakin				
No	12(31.58%)	48(77.42%)	**0.035**	**1.0**
Yes	26(68.42%)	14(22.58%)		**3.28(1.08-10.5)**
Tegretol				
No	33(86.84%)	23(37.1%)	**0.002**	**1.0**
Yes	5(13.16%)	39(62.90%)		**0.12(0.03-0.44)**
Rivotal				
No	28(73.68%)	55(88.71%)	0.262	1.0
Yes	10(44.74%)	7(11.29%)		1.95(0.6-6.32)

DISCUSSION

The present study aimed to evaluate the hematological indices in discriminating between focal and generalized onset epilepsy.

According to the results of the study, out of 16 hematological parameters only MPV showed a significant association with generalized epilepsy in multivariate analysis. In agreement with the present study is an Iranian studyincluding 199 patients with epileptic seizure to assess the platelet volume indices in different types of seizure. There were 59 attacks were focal seizures and 149 attacks with generalized convulsive seizures. The MPV was significantly higher as compared to the focal onset (9.82±1.10 ft vs. 9.51±1.04 ft, p=0.050) (11). In another study, Ozaydin *et al.*, (10) used ROC curve to evaluate the discriminative value of MPV in differentiation between simple and complex febrile seizure in 493 Turkish children. The mean MPV in patients with complex febrile seizure was 7.99 ±0.96 fL compared with (8.77 ±0.75) in patients with simple febrile seizure with a highly significant difference (p=0.001). ROC curve analysis revealed that the optimum MPV level cut-off points was 8.25 fL with

a sensitivity and specificity of 60% and 80% respectively (AUC=0.72).

The association of MPV with generalized epilepsy cannot be attributed only to the to the role of platelets in inflammation as indicated in most literatures. Eroglu *et al.,* (4) stated that MPV elevation without a significant change in the number of platelets could reflect the ongoing inflammatory condition. Increased MPV is supposed to be a marker of platelet activation, and larger platelets can be prothrombotic and may aggregate more easily. However, there should be another role for this marker, because in view of inflammation, the NLR is more robust indicator than MPV. Interestingly, NLR had no significant association with the type of epilepsy in the present study even in univariate analysis.

Alternatively, few drugs for treatment of generalized epilepsy do induce thrombocytopenia (12, 13). This was evidenced in the present study although the difference between focal and generalized onset group in platelet count was not significant. Thus, thrombocytopenia induces the bone marrow for increased production of thrombocytes. These new thrombocytes are larger in mean size which may be a potential reason for the increase in MPV. Accordingly, the present result cannot be generalized as a tool for differentiation between focal and generalized onset epilepsy and should be interpreted with caution.

Also, in line with the present study, Eroglu *et al.,* (4) did not find a significant association between NLR and the occurrence of seizure or with the type of seizure attack. However, some previous studies detected a strong association between NLR and epileptic seizure (14). Yiğit *et al.,* (8) revealed a significant increase in the NLR levels in complex febrile seizures compared with that in simple febrile seizures.

The current study disclosed an increase in sodium levels in generalized onset seizure compared with focal onset. The exact mechanism for this although not known could be related to the rate of cellular damage during generalized type compared to focal type of epilepsy with the subsequent release of sodium ion for died cells into extracellular space.

CONCLUSION

Collectively, these data indicate the possible utility of MPV in the discrimination between generalized and focal onset epilepsy. However, the result should be interpreted with caution because such association may be due to the side effects of some antiepileptic drugs. On the other hand, the NLR has no value in differentiation between the two types of epilepsy (generalized and focal onset epilepsy).

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest for this study.

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