European Review for Medical and Pharmacological Sciences 2014; 18: 3380-3385

Neutrophil-to-lymphocyte ratio and red blood cell distribution width is a practical predictor for differentiation of febrile seizure types

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Abstract. – OBJECTIVE: Febrile seizures (FS) are the most common neurological emergency in childhood. They are divided into two groups accordingly clinical features, simple febrile seizure and complex febrile seizure. Until now laboratory tests have not been used as a parameter of classification of them. The objective of this study is to estimate the usefulness of the hematogical parameters especially neutrophil-to-lymphocyte ratio (NLR) and red blood cell distribution width (RDW) in the differentiation of febrile seizure types.

PATIENTS AND METHODS: A retrospective review was conducted on patients from 6 months to 6 years old presenting with first febrile seizure admitted to a tertiary care hospital. Epidemiological and laboratory variables of the patients were collected.

RESULTS: The mean NLR in the simple FS and complex FS groups was 2.18 ± 1.9 and 3.8 ± 4.2 respectively, and the difference was significant (p = 0.024). The mean serum red blood cell distribution width in the simple FS and complex FS groups was 16.1 ± 1.1 and 16.6 ± 0.8 respectively, and the difference was significant (p = 0.019). NLR and RDW values in complex FS patients were statistically higher than simple febrile patients. ROC analysis showed that if the chosen cut-off point for NLR is 1.98 the sensitivity and specificity are 66.7% and 60.3% respectively. These were statistically significant (p = 0.040 AUC 0.623, CI 0.503-0.743). If the chosen cut-off point for RDW is 16.350, the sensitivity and specificity are 59.0% and 58.6%, respectively. These were statistically significant (p = 0.037 AUC 0.626, CI 0.515-0.736) too.

CONCLUSIONS: NLR and RDW were simple, effective and practical predictors for differentiation of FS types. They will have potential values in public health practice for management of FS patients.

Key Words:
Children, Convulsion, Febrile seizure, Neutrophil-to-lymphocyte ratio, Red blood cell distribution width.

Introduction

Febrile seizures are most common cause of convulsions in young children. They associated with an elevated temperature greater than 38°C, the patient is typically between the ages of six months and six years and with no triggers for seizures, central nervous system infection or inflammation. FS is mostly short and self-limiting, and with no recurrence or squeal[1]. Febrile seizures are divided into two groups as simple FS and complex FS according to their clinical features. Simple FS are generalized seizures, lasting less than 10 min and single episodes during the same febrile event. Complex FS are focal semiology, lasting more than 10 minutes and occurring twice or more within the same febrile episode[2,3]. In children with simple FS, the risk of central nervous system infection is very low compared to those with complex FS[4,5]. In addition to, children with complex febrile seizures have a higher risk for later development of epilepsy[6]. The risk was found up to 21-49% in children with complex febrile seizure[6,7]. Mostly the classification of FS is made easily with clinical features but sometimes the duration or type of seizure could not be described very clearly by parents of the patient. In such patients, laboratory tests may help the classification. We hypothesized that some blood parameters, especially NLR and RDW, may be changed according to the seizure's type. The challenge is to determine when the classification of a febrile seizure with laboratory parameters is useful.

Materials and Methods

Study Population

Data were collected in 112 patients with febrile seizure. Children with a first diagnosis of

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FS on or after age 6 months up to 6 years (70 months) of age from January 1, 2011 through December 31, 2012 were identified among the cohort members. The medical records of 112 patients who diagnosed with febrile seizure were screened in that period. Fifteen patients were excluded because their laboratory outcomes were inadequate. A diagnosis of FS was determined based on International Classification of Diseases Ninth Revision (ICD-9) codes (ICD-9 780.31, 780.32) identified in either an Inpatient or Emergency Department settings. The study was approved by the local Ethics Committee and followed the Declaration of Helsinki for research involving human subjects.

The patients were divided into two groups: the simple febrile seizure group and complex febrile seizure group. Simple FS was defined as a single seizure that last less than 10 minutes, occur once in a 24-hour period and have no focal features. Complex FS was defined as episodes that last more than 10 minutes, occur more than once in 24 hours or have focal features or postictal paresis.

Exclusion criteria were applied on seizures with fever in children who had known to have central nervous system abnormalities, metabolic disturbances, history of afebrile seizures, and previous evidence of intracranial infection, previous neurologic insults.

Laboratory Analysis

White blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), red blood cell distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), the number of neutrophils and lymphocytes as well as the percentages of neutrophils and lymphocytes, neutrophil/lymphocytes ratio (NLR) in peripheral blood samples at the time of the first evaluation were recorded. NLR was calculated by dividing the percentage values of neutrophils and lymphocytes obtained.

Statistical Analysis

Parametric data are expressed as mean ± SD and categorical data as a percentage. SPSS 16.0 (SPSS, Chicago, IL, USA) was used to perform a statistical analysis. Independent parameters were compared via independent-samples *t*-test. Mann-Whitney U-test was used to test parametric data without a binomial distribution. Categorical data were evaluated using the chi-squared test where appropriate. $p < 0.05$ was accepted as significant.

Results

Ninety-seven (97) patients with febrile seizure admitted to our clinic between 2011 and 2012 were included in the chart review. The mean age of the simple FS group (n=58) was 30.7 ± 18.3 months, and 38 (65.5%) were males. The mean age of the complex FS group (n=39) was 25.2 ± 16.7 months, and 21 (53.8%) were males. No significant differences were found between the groups in terms of age and gender (all $p > 0.05$).

There was a significant difference in results of NLR and RDW among simple febrile seizure group and complex febrile seizure group. The mean NLR in the simple FS and complex FS groups was 2.18 ± 1.9 and 3.8 ± 4.2 respectively, and the difference was significant ($p = 0.024$). The mean serum red blood cell distribution width in the simple FS and complex FS groups was 16.1 ± 1.1 and 16.6 ± 0.8 respectively and the difference was significant ($p = 0.019$). There was no significant difference in other complete blood count parameters, serum C-reactive protein values and erythrocyte sedimentation rate values. The characteristics and laboratory data of the groups are shown in Table I.

ROC analysis showed that if the chosen cut-off point for NLR is 1.98, the sensitivity and specificity are 66.7% and 60.3%, respectively. These were statistically significant ($p = 0.040$ AUC 0.623, CI 0.503-0.743). Although, if the chosen cut-off point for RDW is 16.350, the sensitivity and specificity are 59.0% and 58.6%, respectively. These were statistically significant ($p = 0.037$ AUC 0.626, CI 0.515-0.736) (Figure 1).

Discussion

This is the first report investigating the relationship between febrile seizure types and serum complete blood count parameters in children. The major findings of the present study were: neutrophil-to-lymphocytes ratio and red blood cell distribution width values in patients with complex febrile seizure were significantly higher than those patients with simple febrile seizure. The NLR of 1.98 seems to be the most useful

Table I. Relationships between clinic and laboratory characteristics of febrile seizure groups.

	SFS group (n= 58)	CFS group (n= 39)	*p* value
Age (months)	30.7 ± 18.3	25.2 ± 16.7	0.135
Gender			
Male	38 (65.5 %)	21(53.8 %)	0.251
Female	20 (34.5 %)	18 (46.2 %)	
WBC (× 10^3/mm^3)	11.3 ± 6.1	10.8 ± 4.5	0.642
RBC (10^6/mL)	4.6026 ± 0.47	4.5395 ± 0.57	0.575
Neutrophil count (× 10^3/mm^3)	6.1 ± 3.9	6.7 ± 4.0	0.510
Neutrophil (%)	53.17 ± 19	59.94 ± 21.68	0.117
Lymphocytes count (× 10^3/mm^3)	4.1 ± 3.5	3.1 ± 2.3	0.093
Lymphocytes (%)	37.81 ± 17.75	31.19 ± 19.87	0.098
NLR	2.18 ± 1.91	3.89 ± 4.28	0.024
Hb (g/dL)	11.7 ± 1.1	11.8 ± 1.6	0.753
Hct (%)	35.4 ± 4.9	34.7 ± 4.4	0.516
PLT (109/L)	315.017 ± 134.220	285.487 ± 130.100	0.282
MCV (fl)	75.87 ± 5.86	76.61 ± 4.36	0.477
MPV (fl)	7.47 ± 0.95	7.50 ± 0.95	0.906
RDW (%)	16.12 ± 1.11	16.60 ± 0.86	0.019
CRP mg/dl	25.47 ± 37.78	35.20 ± 43.58	0.308
ESR (mm/h)	13.25 ± 8.5	18.0 ± 11.1	0.574

Values are expressed as mean ± standard deviation. SFS: simple febrile convulsion, CFS: complex febrile seizure.

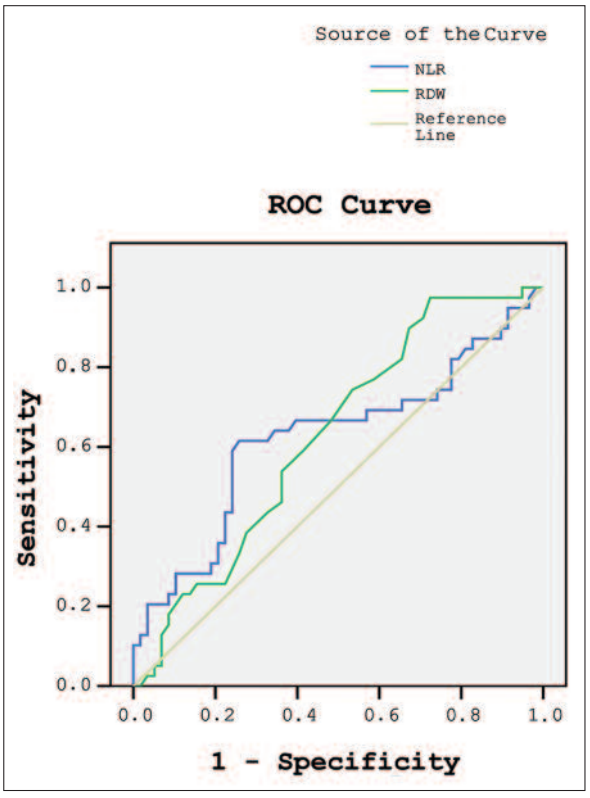

Figure 1. ROC curves of neutrophil-lymphocyte count ratio (NLR) and red blood cell distribution width (RDW) for discriminating simple febrile seizure from complex febrile seizure. The area under the curve for RDW (AUC, 0.626; 95% CI, 0.515-0.736) was greater than that for NLR (AUC, 0.623; 95% confidence interval [CI], 0.503-0.743).

cut-off value in the differentiation of febrile seizure in children. Febrile seizure is a convulsion that is associated with an elevated temperature greater than 38°C in a child younger than six years of age without central nervous system infection or inflammation, acute systemic metabolic abnormality, and history of previous afebrile seizures. Febrile seizures occur in 2 to 5 percent of children in that age group[3].

Febrile seizures have two types according to its clinical features: simple and complex febrile seizure. Simple febrile seizure is the most common type and is characterized by seizures that last less than 10 minutes, occurs once in a 24-hour period, and has no focal features. Complex febrile seizure is characterized by episodes that last more than 10 minutes, occurs more than once in 24 hours or has focal features or postictal paresis[3]. Some etiological factors were hold responsible such as: fever induced factors like interleukin-1 beta, viral infections, immunization, low gamma-aminobutyric acid (GABA) levels in cerebrospinal fluid (CSF), iron insufficiency and genetic susceptibility[8-14].

Diagnostic testing is unnecessary in most patients with simple febrile seizures. Neuroimaging, laboratory testing, and electroencephalography are required only in specific circumstances. Lumbar puncture (LP) should be only considered when: (1) there are meningeal signs or symptoms that suggest a possible meningi-

tis; (2) in infants between 6 and 12 months if the immunization status for *Haemophilus influenzae* type B or *Streptococcus pneumoniae* is deficient or undetermined; (3) when the patient is on antibiotics because antibiotic treatment can mask the signs and symptoms of meningitis[15]. LP should also be considered when the clinician remains concerned about possible intracranial infection, or when febrile seizures occur after the second day of illness. Also febrile status epilepticus may be another possible indication for lumbar puncture[16,17].

The prognosis of febrile seizures is favorable in children. There is a small excess in mortality among children with febrile seizures, especially with complex febrile seizures[18]. Additionally, neurologic complications occurred only after complex or prolonged febrile seizures. Nelson et al[19] found that children with abnormal neurologic development and whose first seizure was complex had a risk 18 times of afebrile seizures by seven years of age than that in children with no history of febrile seizures. Annegers et al[7] observed children with a history of febrile seizures into adulthood, and they determined three risk factors for developing epilepsy: focal seizures, prolonged seizures, and repeated episodes within 24 hours.

The red blood cell distribution width and neutrophil-to-lymphocyte ratio are increased in various inflammation-related diseases, but their clinical significance in febrile seizures has not been reported. We found a significant association between the NLR and complex FS. NLR, which is calculated as the absolute count of neutrophils divided by the absolute count of lymphocytes, is an inflammation index that can be easily detected from a complete blood count. In recent studies, abnormal NLR has been reported to be associated with cardiovascular disease[20,21], brain vascular disease[22], liver disease[23], autoimmune disease[24,25], familial mediterranean fever[26], and cancer[27,28] previously. The mechanism underlying this association of NLR with complex FS has not been elucidated, but it may depend on the interleukin 1 beta induction of the fever, of the neutrophilia, and of the migration of neutrophils into tissues[29].

Red blood cell distribution width is a routinely tested index to describe size variations of red blood cells, and has been widely used in investigating the etiology of anemia[30]. It has been reported to be positively correlated with inflammatory markers such as the erythrocyte sedimentation rate, CRP and inflammatory cytokines in various diseases[31,32]. Therefore, it is often considered as an inflammatory marker. Recent studies have revealed that RDW is an effective diagnostic and prognostic predictor of various diseases such as cardiovascular disease[33-35], liver disease[36,37], brain vascular disease[38], septicemia[39], and cancer[40]. RDW was found to be associated with incident myocardial infarction independent of cardiovascular risk factors and anemia[41]. Huang et al[42] investigated that heart failure patients with higher RDW have a poorer prognosis than those with lower RDW. Chen B et al[37] showed that: RDW also can predict fibrosis and cirrhosis in chronic hepatitis B patients with relatively high accuracy. RDW is also associated with poor survival of lung cancer patients and with high mortality in patients with sepsis[39,40]. Although the exact mechanisms that underlines the association between RDW and these diseases remain unknown, it is speculated that inflammation may be a connection between them.

Presently, classification of febrile seizure depends on the clinical signs and symptoms. Compared with these conventional tools, RDW and NLR have some advantages. They are more objective and easily acquired without needing additional costs, routinely available and inexpensive in clinical practice. Altogether, RDW and NLR are useful indices to assess the types of FS.

This study has several strengths. First, it is a novel study that investigated the association between laboratory parameters and types of febrile seizure in children. We determined a cutoff value for neutrophil-to-lymphocytes ratio of 1.98. It can be useful for classification of the type of febrile seizure, especially if the history of the convulsion was not clear.

However, we would like underline that this study with has a relatively small sample size. Moreover, subtypes of lymphocytes and other indicators of the immune system such as cytokines were not investigated.

Conclusions

We have demonstrated that NLR and RDW were increased in complex FS patients and they seem to be a sensitive parameter to evaluate the type of febrile seizure.

Further studies are needed to explore the potential mechanisms underlying this association.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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