IMMUNOLOGICAL PROFILE COMPARISON IN PATIENTS WITH FEBRILE CONVULSION

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Abstract

*The neutrophil-lymphocyte count ratio (NLCR) has been identified as a predictor of bacteremia in medical emergencies. The aim of this study was to investigate the value of the WBC count,neutrophil,NLCR,CRP in patients with simple febrile convulsions.**Methods:** Consecutive pediatric patients were retrospectively studied from those admitted with febrile convulsions and few of those admitted with viral fever without convulsions. Association of convulsions with NLCR was compared with C-reactive protein (CRP), neutrophil count, white blood cell (WBC) count. The study consisted total of 100 patients,70 patients had simple febrile convulsion and 30 had fever without convulsions.**Results:**NLCR was significantly more in febrile convulsion patients(p=0.026) **Conclusion:** NLCR is higher in patients with febrile convulsion indicating enhanced immune reaction..*

Keywords - *neutrophil-lymphocyte ratio,pediatric,febrile convulsion,CRP*

1.INTRODUCTION

Seizure is the most common neurological disorders in children, where, 4-10% cases experience at least one seizure before the age of 16 years.

Febrile seizures are seizures that occur between the age of 6 and 60 mo with a temperature of 38°C (100.4°F) or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures[1]. A simple febrile seizure is a primary generalized, usually tonic–clonic, attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-hr period[1]. A complex febrile seizure is more prolonged (>15 min), is focal, and/or reoccurs within 24 hr[1]. Febrile status epilepticus is a febrile seizure lasting longer than 30 min[1].

The exact cause of this disorder is not known,but various studies indicate the potential role of genetic and environmental factors[2].Febrile seizure is more dangerous in focal,lateralized or prolonged cases, especilly in cases that last for more than 1h,or a seizure limited to one part of the body,and a seizure that occurs more than once within 24h[3]. Measuring laboratory markers in patients is important. Considering the importance of children's health,the present study was conducted to determine the role of inflamatory marker.

In Immuno-competent patients, white blood cell populations play an important role in the systemic inflammatory response to infection. Following endotoxemia the number of circulating neutrophils increases while lymphocyte counts decrease. The occurence of Neutrophilia is well recognized as infection marker. Absolute lymphocytopenia as a possible marker in infectious disease management is not routinely considered. Absolute lymphocytopenia is considered recently in several conditions now a days. Combining both parameters seems a logical step and the ratio of neutrophil and lymphocyte counts is increasingly used in several clinical circumstances. Initially, this so-called neutrophil-lymphocyte count ratio (NLCR) was studied as an infection marker in ICU patients in adults and found to correlate well with disease severity and outcome, according to APACHE-II and SOFA scores[4]. Other studies focused on the use of the NLCR in specific clinical conditions, like appendicitis, or its use as an independent predictor of survival in patients with various conditions ranging from oncological to cardiovascular diseases[5]. In a retrospective study, the NLCR proved to

be a simple and even better marker in predicting bacteremia than routine parameters, like white blood cell (WBC) count and C-reactive protein (CRP) level, in infectious emergency admissions[6].

Efforts are currently underway to improve the prognostic value of these clinical scales. In infections like pneumonia which is a localized infectious process that causes a systemic inflammatory response, it is postulated that the study of this inflammatory process would assist in evaluating the severity of community acquired pneumonia and predicting its progress. In this respect, several biomarkers in various illnesses have been studied, including procalcitonin (PCT), proadrenomedullin (proADM) and copeptin[7,8]; these molecules measured at diagnosis have shown a greater prognostic power than C-reactive protein (CRP) or total leukocyte count, but have not proven to be superior to traditional scales. Several authors have reassessed the use of simpler, more accessible markers at diagnosis, such as the neutrophil/lymphocytes ratio (NLR)[6,9] or the neutrophil count percentage (NCP)[9],with the advantage that both are easily identifiable, inexpensive parameters.

Along these lines,Curbelo et al.[9] compared NCP with PCT, proADM, and copeptin, and found it was not significantly inferior in terms of its prognostic capacity for mortality in the short and medium term. Continuing in the search for efficient biomarkers, other authors have proposed simple, economic parameters and evaluated their usefulness not only for diagnosis, but also for the follow-up of patients.

2.Materials and Methods

This was a retrospective study of patients with simple febrile convulsions and patients with fever with simple viral fever without convulsions or central nervous system involvement, admitted to our hospital,in department of paediatrics, from June 2019 to December 2019. The study protocol was approved by the Clinical Research Ethics Committee of the same center.

The inclusion criteria were: age<18 years at the time of diagnosis and hospitalization. We determined that both the admission and discharge reports listed the primary diagnosis as simple febrile convulsion and viral fever. Total leukocytes and differential counts were determined from peripheral blood in EDTA, and by fluorescence flow cytometry and hydrodynamic focusing (forward and side scatter with a Sysmex XE-2100TM automated hematology analyzer (Sysmex, Kobe, Japan).

We excluded patients who had subsequent evidence of central nervous system involvement, family history of afebrile convulsions, complex febrile convulsion/ febrile status epilepticus. Other exclusion criteria included the presence of active hematologic or oncologic disease and severe immunodeficiency.

All patients were classified using socio-demographic characteristics, comorbidities, and treatment were systematically recorded. In addition, clinical and laboratory variables associated were recorded. Patients were treated according to the routine clinical practice. The main outcome variable was NLCR and correlation to WBC,CRP,ESR.

1.1Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven`s test for homogeneity of variance has been performed to assess the homogeneity of variance.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small.

Pearson correlation between study variables is performed to find the degree of relationship, Pearson correlation co-efficient ranging between -1 to 1, -1 being the perfect negative correlation, 0 is the no correlation and 1 means perfect Positive correlation

A. Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value:0.01<P ≤ 0.05)
** Strongly significant (P value : P≤0.01)

2. Results and analysis

Table 1: Age distribution of patients studied

Age in years	**No. of patients**
Up to 1yr	19
1-2yrs	37
3-6yrs	44
Total	100

Most of the patients included were in the age group of 3-6 years

Table 2: Gender distribution of patients studied

Gender	**No. of patients**
Female	42
Male	58
Total	100

Study included 42% of females and rest were males

Table 3: Blood investigations

variables	**No. of patients (n=50)**	**%**
Hemoglobin (g/dl)		
● <12	76	76.0
● 12-16	24	24.0
● >16	0	0.0
PCV		
● <30	26	26.0
● 30-40	68	68.0
● >40	6	6.0
Total Count		
● <4000	4	4.0
● 4000-11000	38	38.0
● >11000	58	58.0

About 76% of the patients had Hb <12 g/dL. Most of the patients had elevated total counts of >11,000 c/mm^3.

Table 6: h/o convulsions distribution of patients studied

H/o convulsions	**No. of patients**	**%**
No	30	30.0
Yes	70	70.0
Total	50	100.0

70 patients had convulsions, out of 100 patients.

Table 7: Comparison of clinical variables according to ICU stay of patients studied

variables	**ICU**		**P value**
	No	**Yes**	
Hemoglobin (g/dl)	12.08±1.38	9.49±1.87	<0.001**
PCV	36.51±3.94	30.79±5.82	0.001**
Total Count	9247.93±2506.02	16377.43±7870.95	0.001**
Neutrophils	60.07±13.32	67.40±18.46	0.171
Lymphocytes	35.27±13.2	28.77±17.63	0.207
Monocytes	2.83±1.70	3.41±2.13	0.407
Basophils	3.00±1.41	2.00±1.22	0.077+
Eosinophils	2.65±0.84	3.98±1.77	0.008**
Platelet count	17.13±7.90	45.43±38.17	0.007**
ESR	2.45±2.50	4.30±4.08	0.112
NLCR	12.73±9.48	22.12±14.55	0.026*
CRP	12.08±1.38	9.49±1.87	<0.001**

Total count was elevated significantly in patients with h/o convulsions. Average total count of patients with convulsions was 16377(p=0.001)
Neutrophil count was not significantly different in either groups.
NLCR was significantly more in convulsion patients(p=0.026).CRP was more in patients with convulsions in our study.

Table 8: Pearson correlation

Pair	**r value**	**P value**
CRP **vs** Total Count	0.107	0.460
CRP **vs** Neutrophils	0.006	.0965
CRP **vs** Lymphocytes	0.004	0.978
CRP **vs** ESR	-0.042	0.771
CRP **vs** NLCR	0.046	0.751

Correlation coefficient of CRP was seen here. There was no significant positive correlation between CRP and total count. CRP and NLCR did not correlate to well.

Table 9: Pearson correlation

pair	**r value**	**P value**
NLCR **vs** Total Count	0.577	<0.001**
NLCR **vs** Neutrophils	0.848	<0.001**
NLCR **vs** Lymphocytes	-0.827	<0.001**
NLCR **vs** ESR	0.229	0.110

NLCR had good correlation with total count($p<0.001$), neutrophils($p<0.001$) and negatively correlated with lymphocytes($p<0.001$)(fig3)

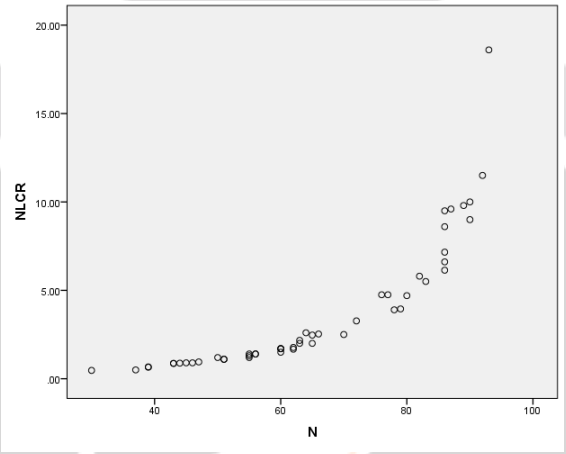

Fig 3: NCLR vs Neutrophil count

3.Discussion

Recently, the NLCR has been ‘‘rediscovered’’ as a simple, promising marker in several clinical circumstances. The discriminatory capacity of the NLCR in febrile convulsion patients outweighed predictive values of traditional biomarkers. Increased NLCR values were seen in patients with increased ion risk. The AUC of the NLCR.ROC curve was significantly higher than that of conventional markers, especially CRP..The host inflammatory response in the development of convulsion has gained growing interest and infection markers are increasingly used to facilitate treatment decisions and improve the accuracy of clinical severity scores in patients admitted. ‘‘Old’’ markers like CRP, WBC count and neutrophil count are still the most frequently used infection markers in daily clinical practice. Although recently introduced infection markers such as procalcitonin, several cytokines and markers like endothelin-1, copeptin and pro-adrenomedullin show promising results in risk assessment and outcome prediction the implementation of these ‘‘new’’ infection markers is hampered by validation, costs and accessibility.In various stressful events the physiological response of circulating leucocytes is characterized by an increase in neutrophil counts and a decline in lymphocyte counts. Neutrophilia is caused by demargination of neutrophils, delayed apoptosis of neutrophils and stimulation of stem cells by growth factors. Margination of lymphocytes, redistribution of lymphocytes and marked accelerated apoptosis are supposed mechanisms of the observed lymphocytopenia in infectious emergencies.

Lymphocytopenia has shown promising results in the prediction of bacteremia in infectious emergency admissions. Although relatively unknown as a marker of disease severity or prognosis, lymphocytopenia has been described, especially in the acute phase and probably limited to T-cells and T-cell subsets. It is hypothesized that depression of absolute peripheral blood T-cell counts represents the shift of these cells towards the infective foci in order to be sequestered in protective mechanisms. The mean lymphocyte count in our overall study population was just above the lower limit of normal.

In the current retrospective study, we further explored the value of the NLCR in patients admitted with simple febrile convulsions.

Our current study adds to the value of the NLCR by showing that this marker is of interest in patients admitted to the ED with fever. In our opinion the novelty of the NLCR is the possibility of implementing this parameter simply by using already available biomarkers (WBC-count, neutrophil count and lymphocyte count). Since calculating the NLCR is easy to do and does not require additional testing it may add to our ability to predict mortality. Diagnosing and subsequently assessing prognosis, severity and site-of-care indicators remains a challenging process.

It could be of interest to investigate whether adding the NLCR to currently existing severity scores would improve the overall performance of these scores thereby assisting the emergency physician in the treatment options. Use of the NLCR may allow the clinician to stratify patients with CAP into different prognostic categories and could possibly add to the performance of wellaccepted severity-of-illness scores.This study has several limitations. First, in view of the minor differences between the AUC for neutrophil numbers and NLCR, the NLCR may simply reflect differences in neutrophil numbers.Second, as this is a single centre study the results should be validated in other settings. Third, recently developed infection markers (procalcitonin, pro-adrenomedullin, neopterin) were not evaluated. Fourth, in general biomarkers alone are clearly less suited in the prediction of prognosis and severity of disease.

4.Conclusion

NCP and NLR are accessible, inexpensive parameters that provide information on the prognosis of patients with fever when analyzed in early follow-up.NLCR proved to be a simple and even better marker in predicting bacteremia than routine parameters, like white blood cell (WBC) count and C-reactive protein (CRP) level, in infectious emergency admissions.

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