Original Article

Can we predict occurrence of febrile convulsions in children with fever by increased neutrophil-to-lymphocyte ratio and C-reactive protein?

Rajakumar Marol[1], Rohitkumar Marol[2], Sharanabasappa Matti[3], Renuka Marol[4]

From [1]Senior Consultant, Department of Pediatrics, Shivajyoti Institute of Child Health, Haveri, Karnataka, India, [2]Undergraduate, Department of Neuroscience, University of Rochester, New York, USA, [3]Professor, Department of Pediatrics, Koppal Institute of Medical Sciences, Koppal, [4]Consultant, Department of Pediatrics, Shivajyoti Institute of Child Health, Haveri, Karnataka, India

ABSTRACT

Background: Febrile seizure (FS) is the most common seizure disorder in children and is a major challenge in pediatric practice because of its high incidence in young children, a lack of predictive indications and their tendency to recur. Age at first seizure, male sex, and family history of FS, duration of fever, and height of temperature are the only significant risk factors presently known for predicting FSs. **Objectives:** The objectives of the study were to determine whether alterations in basic laboratory parameters such as neutrophil-to-lymphocyte ratio (NLR) and serum C-reactive protein (CRP) are associated with first episode of FS in children. **Materials and Methods:** This retrospective observational study was conducted in a level 2 pediatric hospital. A total of 196 children between the age of 6 months and 60 months who presented with first episode of febrile convulsions constituted the study group (FS cases). A total of 196 febrile children who presented only with fever within the same time period were selected as controls. NLR, CRP, and other basic laboratory parameters were compared between FS cases and controls. **Results:** NLR and CRP were both higher among FS than controls. Median of NLR in FS and controls was 1.55 and 0.67 ($p<0.001$). Median CRP in FS and controls was 10.85 and 4.85 mg/dl, respectively ($p<0.001$). **Conclusions:** High suspicion of FS may be warranted in febrile children with raised NLR and CRP, and hence, these parameters may be considered as predictors for developing first episode of seizures in febrile children.

Key words: C-reactive protein, Febrile convulsions, Neutrophil-to-lymphocyte ratio, Predictors

Febrile seizures (FSs) are the most common seizure disorder in childhood. High incidence in young children and high rate of recurrence make them a major challenge in pediatric care. FSs are defined as seizures in association with fever more than 38°C (100.4°F), in children who do not have evidence of an intracranial cause, any other cause for seizure and a history of an afebrile seizure [1-3]. FSs are more commonly observed in males with a male:female ratio of 1.6:1 [4-6]. FSs affect 2–5% of children in Western countries with a peak incidence between 12 and 18 months [7,8]. It is more frequently seen in the Indian population affecting 5–10% of children [9]. Lack of immunization against H influenza and pneumococcal vaccine might increase the risk of bacteremia and convulsions in young children in developing countries [10].

Typically, FS occurs in children aged 6 months–60 months. The enhanced neuronal excitability of the maturing brain because of elevation of body temperature predisposes the child to seizures which can occur because of concurrent effects of enzymes, ion channels, and receptors. Studies have also noted that trace elements such as iron, zinc, magnesium, selenium, and copper can play a role in these convulsions [11]. Studies have shown that inflammatory cytokines interleukin (IL)-B, IL-6, and tumor necrosis factor (TNF) alpha can play major role in the generation of FS [12]. Although inflammatory cytokines are useful biomarkers, the drawbacks are their high cost and limited availability. However, low cost inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR) and serum C-reactive protein (CRP) have gained increasing attention as independent predictors of FS.

The American Academy of Pediatrics says that routine blood tests usually are unnecessary if history and physical examination are typical that of a FS [13,14]. However, Warden *et al*. have recommended routine white blood cell (WBC) assessment for children with FS in their systematic review [15]. NLR is an inexpensive, easily accessible, and easily calculable parameter based on complete blood count (CBC) and it is a measure of

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Correspondence to: Dr. Rajakumar Marol, Department of Pediatrics, Shivajyoti Institute of Child Health, Heggeri Road, Haveri - 581 110, Karnataka, India. E-mail: dr.rajakumar71@gmail.com

systemic inflammation [16]. Serum CRP is an acute-phase reactant of inflammation and its increase is highly sensitive and moderately specific in identifying bacterial infections [17]. According to McCarthy, the evaluation of an ambulatory, febrile child should include at least determination of CRP [18]. Biyani *et al*. said that any child with FS with a high CRP value should be evaluated for the infection and it is an initial good tool in evaluating the cause of fever in all these children [19].

It is difficult to predict which children with fever are going to have convulsions. This creates stress and anxiety in parents and often chaos in hospital. The age at first seizure, male sex, family history of FS, duration of fever, and height of temperature are considered as significant predictors for FSs. In the present study, we have tried to know whether low cost laboratory parameters such as NLR and CRP can be considered as predictors for developing FSs in children with fever.

MATERIALS AND METHODS

This retrospective observational case–control study was conducted in a level 2 hospital catering mainly children from rural and low socioeconomic background. Children between the ages of 6 months and 60 months who attended outpatient department (OPD) were included by time bound convenient sampling method over a period of 3 years from April 1, 2017, to March 31, 2020. Children, presented within 48 h of fever with first episode of convulsions and who were tested for CBC and CRP, were included in the study. Those who were febrile for more than 48 h, who had taken antibiotics before attending hospital, who had suspicion of meningitis, who had convulsions in the past, and those who were not tested for CBC and CRP were excluded from the study. An equal number of children aged 6 m–60 m who presented with fever without convulsions and were tested for CBC and CRP were selected as controls.

CBC and CRP tests were done routinely for all children with and without FS and without identifiable source of fever. The laboratory reports retrieved from the hospital software were collected and analyzed for differences between FS and controls in the following parameters: Hemoglobin (Hb), total leukocyte count (TC), neutrophils, lymphocytes, NLR, and CRP. NLR was calculated by dividing the neutrophil percentage by lymphocyte percentage. NLR does not differ in its value by calculation either with the absolute count or percentage of cells.

The study was conducted as per the recommendations of the Institutional Ethical Committee and in confirmation with the Declaration of Helsinki. For statistical analysis, a non-parametric Mann–Whitney U-test was applied to compare the parameters between cases and controls. Statistical significance was defined as $p<0.05$.

RESULTS

Out of 281 children who presented with FS during study period, 196 children (cases) were eligible for the study. A total of 196 sex-matched children who presented with short duration fever without convulsions and who were also tested for CBC and CRP were selected as controls. Out of 392 children, the majority (75%) belonged to the age group of 6 months–24 months. In both the groups, 123 (62.75%) were male and 73 (37.25%) were female, with ratio (male:female) of 1.68:1 (Table 1).

Values for age are expressed in mean±standard deviation. Total percentage refers to proportion with respect to the whole study population.

In our study, TLC, polymorphs, NLR, and CRP were significantly high in case compared to control group, whereas lymphocytes were high in the control group (Table 2). Notably, lymphocytes were lower among FS than controls; NLR was higher among cases than in controls and CRP was higher among cases than among controls.

DISCUSSION

In our study, we compared NLR and serum CRP level in febrile children with and without FS who attended OPD of a level 2 pediatric hospital over a period of 3 years. Majority of the children with FS were below 2 years of age. Fetveit, in their study, had the peak incidence of FS at 18 months of age with male predominance [20]. Similar results were also observed by Gontko-Romanowska *et al*. and Sharawat *et al*. [21,22]. Since anemia was prevalent in both FS and controls with a small difference in mean and median, low Hb and iron deficiency were not found to be an independent contributing factor for FS as observed in other studies by King and King and by Youseffichaijan *et al.* [23,24].

Children with FS had higher TC than febrile children without FS. Higher TC could be because of bacterial infection. Ogawa *et al*. predicted that high WBC count and fever may effectively predict occult bacteremia in pediatric patients with FS [25]. Similar findings were found in other observational studies performed in Iran by Mohebbi *et al*. and in the Netherlands by Van Stuijvenberg *et al*. [26,27]. On the other hand, Toyosawa showed that electrically induced convulsion in rabbits increased peripheral leukocyte counts immediately and remained high 4 h later [28]. Biyani *et al*. also concluded that increased leukocyte count can be due to the stress of convulsions [19].

In our study, we found that children with FS had higher neutrophils and lower lymphocytes compared to controls, contributing to higher NLR among FS than controls ($p<0.001$). Liu *et al*. and Gontko-Romanowska *et al*. also found raised NLR ratio in children with FSs [16,21]. Yazar *et al*. in their findings showed that TLC and NLR were higher in children with FS

Table 1: Age and sex of the patients

Variables	FS group (*n*=196) (%)	Control group (*n*=196) (%)	p– FS versus control
Age (months)	22.82±12.81	16.54±8.55	<0.001
Male	123 (62.8)	123 (62.8)	
Female	73 (37.2)	73 (37.2)	
Total	196 (50)	196 (50)	

FS: Febrile seizure

Table 2: Mean, median, standard deviation, and *P* of different variables in cases and controls

Variables	Group	Mean	Median	SD	p
Hemoglobin	Cases	9.81	9.80	1.21	0.035
	Controls	9.50	9.60	1.14	
Total leukocyte counts	Cases	13.89	12.50	7.12	0.035
	Controls	12.18	11.50	5.65	
Neutrophils	Cases	55.79	57.50	16.74	<0.001
	Controls	39.40	38.00	14.81	
Lymphocytes	Cases	37.38	36.50	16.04	<0.001
	Controls	54.40	56.00	14.79	
C-reactive proteins	Cases	18.38	10.85	17.93	<0.001
	Controls	9.66	4.95	12.26	
Neutrophil-lymphocyte ratio	Cases	2.06	1.55	1.56	<0.001
	Controls	0.91	0.67	0.78	

SD: Standard deviation

than in the control group [29]. These findings suggested that elevated NLR is evidently associated with increased risk of FS in children. Neutrophil-associated inflammation coupled with a decrease in lymphocytes and the anti-inflammatory response could be the driver of this observation [30,31]. The various mechanisms for the same have been explained. Neutrophils play a role in generation of reactive oxygen species, which have been shown to cause epileptic seizures in various studies [32-35]. In addition, neutrophils migrate to the site of injury and drive the secretion of several cytokines, especially, IL-1β and TNF-α, that cause inflammation and contribute to the pathogenesis of FS [36]. In addition, some neutrophils at the site of injury express NaV1.3 sodium channels, which have been genetically linked to epilepsy [37-40]. On the other end of the NLR, a dip in lymphocytes could account for inhibited ability of the body to resist the infection. Thus, NLR proves to be a parametric indication of the complex role in immunity of neutrophils and lymphocytes that could be pathological driver of FS in children.

Increased CRP level ($p<0.001$) was observed in FS compared to controls, which was in accordance with Goksugur *et al*. and Salam *et al*. [41-44]. CRP is an acute-phase reactant, whose synthesis is stimulated by cytokines such as IL-1β and TNF-α. Chen *et al*., in their retrospective study of 910 children who presented to the emergency room with FS, observed that raised CRP levels were an indication for admission [43]. Althaus *et al*. found that the median CRP concentration was higher in the bacterial infections compared with the viral infections [17]. Virta *et al*. had similar results supporting the hypothesis that the cytokine network is activated and could have a role in the pathogenesis of FS [44]. In support of this hypothesis, other inflammatory markers such as copeptin and IL-6 were also raised in children with FS in different studies by Stöcklin *et al*. [45] and Ichiyama *et al*. [46]. This confirms the association between high levels of inflammatory markers and development of fever as a body response to underlying infection and the development of seizure [42]. However, Biyani *et al*. observed no significant difference among the two groups regarding CRP level but a statistically significant difference was observed in leukocyte count [19]. However, Gontko-Romanowska *et al*. showed increased leukocyte count and decreased CRP in children with FSs [21].

The limitations of this study, however, should be acknowledged. As it was a retrospective study based on convenient sampling; especially, for controls, there are potential for biased study group necessitating large multicentric prospective studies. Similar comparison with children of afebrile seizures was not done. Parameters to differentiate between viral and bacterial infections such as blood culture and virological studies for common viral infections such as influenza, adenovirus, parainfluenza, respiratory syncytial virus, and rotavirus were not done. Other contributing factors for FS such as iron and zinc levels were not assessed.

CONCLUSIONS

Authors recommend that children in the age group of 6 months–60 months with fever should be evaluated for CBC and CRP to know the cause of fever; especially, in developing countries, as bacterial infections leading to FSs are very common. Increased NLR and serum CRP may be used as predictors of first episode of FSs in children with fever. This will help in reducing stress and anxiety in parents after the attack of FSs.

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REFERENCES

1. Chungath M, Shorvon S. The mortality and morbidity of febrile seizures. Nat Clin Pract Neurol 2008;4:610-21.
2. Leung AK, Robson WL. Febrile seizures. J Pediatr Health Care 2007;21:250-5.
3. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: Clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics 2008;121:1281-6.

4. Leung AK, Robson WL. Febrile convulsions: How dangerous are they. Postgrad Med 1991;89:217-8, 221-2, 224.
5. Millichap JJ. In: Post TW, editor. Treatment and Prognosis of Febrile Seizures. Waltham, MA: UpToDate; 2020.
6. Millar JS. Evaluation and treatment of the child with febrile seizure. Am Fam Physician 2006;73:1761-4.
7. Canpolat M, Per H, Gumus H, Elmali F, Kumandas S. Investigating the prevalence of febrile convulsion in Kayseri, Turkey: An assessment of the risk factors for recurrence of febrile convulsion and for development of epilepsy. Seizure 2018;55:36-47.
8. Patel N, Ram D, Swiderska N, Mewasingh LD, Newton RW, Offringa M. Febrile seizures. BMJ 2015;351:h4240.
9. Paul SP, Seymour M, Flower D, Rogers E. Febrile convulsions in children. Nurs Child Young People 2015;27:14-5.
10. Chung S. Febrile seizures. Korean J Pediatr 2014;57:384-95.
11. Rehman U, Khan SA, Saldanha PR. Estimation of serum zinc levels in children with febrile convulsions. Int J Contemp Pediatr 2018;5:1518-22.
12. Choi J, Min HJ, Shin JS. Increased levels of HMGB1 and pro-inflammatory cytokines in children with febrile seizures. J Neuroinflammation 2011;8:135.
13. Sadleir LG, Scheffer IE. Febrile seizures. BMJ 2007;334:307-11.
14. Patterson JL, Carapetian SA, Hageman JR, Kelley KR. Febrile seizures. Pediatr Ann 2013;42:249-54.
15. Warden CR, Zibulewsky J, Mace S, Gold C, Gausche-Hill M. Evaluation and management of febrile seizures in the out-of-hospital and emergency department settings. Ann Emerg Med 2003;41:215-22.
16. Liu Z, Li X, Zhang M, Huang X, Bai J, Pan Z, *et al*. The role of mean platelet volume/platelet count ratio and neutrophil to lymphocyte ratio on the risk of febrile seizure Sci Rep 2018;8:15123.
17. Althaus T, Greer RC, Swe MM, Cohen J, Tun NN, Heaton J, *et al*. Effect of point-of-care C-reactive protein testing on antibiotic prescription in febrile patients attending primary care in Thailand and Myanmar: An open-label, randomised, controlled trial. Lancet Glob Health 2019;7:e119-31.
18. McCarthy PL, Jekel JF, Dolan TF. Comparison of acute phase reactants in pediatric patients with fever. Pediatrics 1978;62:716-20.
19. Biyani G, Ray S, Chatterjee K, Sen S, Mandal P, Mukherjee M. Leukocyte count and C reactive protein as diagnostic factors in febrile convulsion. Asian J Med Sci 2017;8:56-8.
20. Fetveit A. Assessment of febrile seizures in children. Eur J Pediatr 2008;167:17-27.
21. Gontko-Romanowska K, Żaba Z, Panieński P, Steinborn B, Szemień M, Łukasik-Głębocka M, *et al*. The assessment of laboratory parameters in children with fever and febrile seizures. Brain Behav 2017;7:e00720.
22. Sharawat IK, Singh J, Dawman L, Singh A. Evaluation of risk factors associated with first episode febrile seizure. J Clin Diagn Res 2016;10:SC10-3.
23. King D, King A. Question 2: Should children who have a febrile seizure be screened for iron deficiency? Arch Dis Child 2014;99:960-4.
24. Youseffichaijan P, Eghbali A, Rafeie M, Sharafkhah M, Zolfi M, Firouzifar M. The relationship between iron deficiency anaemia and simple febrile convulsion in children. J Pediatr Neurosci 2014;9:110-4.
25. Ogawa E, Shoji K, Kamidani S, Miyairi I. Febrile seizures with leukocytosis as a predictor for occult bacteremia. Pediatr Int 2019;69:578-82.
26. Mohebbi MR, Holden KR, Mohammadi M. Peripheral leukocytosis in children with febrile seizures. J Child Neurol 2004;19:47-50.
27. Van Stuijvenberg M, Moll HA, Steyerberg EW, van Gijssel EN, Moons KG, Derksen-Lubsen G. The duration of febrile seizures and peripheral leukocytosis. J Pediatr 1998;133:557-8.
28. Toyosawa K. Changes of peripheral leukocyte-counts by electrically induced convulsion in rabbits (author's transl). Nihon Seirigaku Zasshi 1975;37:297-306.
29. Yazar A, Akın F, Türe E, Çaksen H, Odabaş D. Mean platelet volume and neutrophil-to-lymphocyte ratio may be used as predictors in febrile seizures. J Pediatr Infect Dis 2018;13:283-6.
30. Hernberg M, Mattila PS, Rissanen M, Hansson J, Aamdal S, Bastholt L, *et al*. The prognostic role of blood lymphocyte subset distribution in patients with resected high-risk primary or regionally metastatic melanoma. J Immunother 2007;30:773-9.
31. Brandau S, Dumitru CA, Lang S. Protumor and antitumor functions of neutrophil granulocytes. Semin Immunopathol 2013;35:163-76.
32. Zheng J, Cai J, Li H, Zeng K, He L, Fu H, *et al*. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as prognostic predictors for hepatocellular carcinoma patients with various treatments: A meta-analysis and systematic review. Cell Physiol Biochem 2017;44:967-81.
33. Mantovani A, Cassatella M, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol 2011;11:519-31.
34. Abuhandan M, Calik M, Taskin A, Yetkin I, Selek S, Iscan A. The oxidative and antioxidative status of simple febrile seizure patients. J Pak Med Assoc 2013;63:594-7.
35. Choi BH. Oxygen, antioxidants and brain dysfunction. Yonsei Med J 1993;34:1-10.
36. Haspolat S, Mihçi E, Coşkun M, Gümüslü S, Ozben T, Yeğin O. Interleukin-1beta, tumor necrosis factor-alpha, and nitrite levels in febrile seizures. J Child Neurol 2002;17:749-51.
37. Steinberg BE. Neutrophils: A therapeutic target of local anesthetics? Anesthesiology 2018;128:1060-1.
38. Poffers M, Bühne N, Herzog C, Thorenz A, Chen R, Güler F, *et al*. Sodium channel nav1.3 is expressed by polymorphonuclear neutrophils during mouse heart and kidney ischemia *in vivo* and regulates adhesion, transmigration, and chemotaxis of human and mouse neutrophils *in vitro*. Anesthesiology 2018;128:1151-66.
39. Estacion M, Gasser A, Dib-Hajj SD, Waxman SG. A sodium channel mutation linked to epilepsy increases ramp and persistent current of Nav1.3 and induces hyperexcitability in hippocampal neurons. Exp Neurol 2010;224:362-8.
40. Sun GC, Werkman TR, Battefeld A, Clare JJ, Wadman WJ. Carbamazepine and topiramate modulation of transient and persistent sodium currents studied in HEK293 cells expressing the Na(v)1.3 alpha-subunit. Epilepsia 2007;48:774-82.
41. Goksugur SB, Kabakus N, Bekdas M, Demircioglu F. Neutrophil-lymphocyte ratio and red blood cell distribution width is a practical predictor for differentiation of febrile seizures types. Eur Rev Med Pharmacol Sci 2014;18:3380-5.
42. Salam A, El Sadek S, Abdel-Moneim M, Ahmed ZM, Mo W. Can serum levels of C-reactive protein (CRP), interleukin-6 and copeptin discriminate between simple and complex febrile seizures? INDJ 2016;8:1-11.
43. Chen CY, Yang WC, Wu KH, Wu HP. Clinical assessment of children with first-attack seizures admitted to the ED. Am J Emerg Med 2012;30:1080-8.
44. Virta M, Hurme M, Helminen M. Increased plasma levels of pro-and anti-inflammatory cytokines in patients with febrile seizures. Epilepsia 2002;43:920-3.
45. Stöcklin B, Fouzas S, Schillinger P, Cayir S, Skendaj R, Ramser M, *et al*. Copeptin as a serum biomarker of febrile seizures. PLoS One 2015;10:e0124663.
46. Ichiyama T, Suenaga N, Kajimoto M, Tohyama J, Isumi H, Kubota M, *et al*. Serum and CSF levels of cytokines in acute encephalopathy following prolonged febrile seizures. Brain Dev 2008;30:47-52.

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