Research Article / Özgün Araştırma

DOI: 10.4274/cayd.galenos.2022.32650
J Pediatr Emerg Intensive Care Med 2023;10:1-7

Prediction of Febrile Seizures in Febrile Children with Upper Respiratory Infection

Üst Solunum Yolu Enfeksiyonu Olan Ateşli Çocuklarda Ateşli Nöbetin Öngörüsü

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Abstract

Introduction: Febrile seizures (FS) are the most frequently encountered childhood neurological problems. They cause stress and anxiety for parents and a considerable workload for healthcare providers. The purpose of this study was to identify useful markers capable of predicting the risk of FS in febrile children with upper respiratory infection using complete blood count parameters.

Methods: Four hundred seventy-six children aged between 6 months and 5 years, 240 with a history of first FS, 121 with acute febrile upper respiratory tract infection without seizures (AFI), and 115 healthy controls were included in the study. Two age-and sex-matched control groups were recruited, one consisting of febrile patients without seizures and the other of healthy children.

Results: Logistic regression analysis of all participants together revealed that a hemoglobin (Hb) level ≤10.95 was associated with a 2.937 -fold greater risk of FS, and a neutrophil to lymphocyte ratio (NLR) ≥1.3969 with a 2.719-fold increase in FS (95% confidence interval: 1.885-4.576 vs. 1.873-3.949), (p<0.001).

Conclusion: Although low Hb levels and high NLR can be used to predict the risk of FS, these values alone are not sufficient to predict FS in children with AFI.

Keywords: Febrile seizure, prediction, hemoglobin, neutrophil/lymphocyte ratio

Öz

Giriş: Ateşli nöbetler (FS) çocukluk çağının en sık karşılaşılan nörolojik sorunudur. Ebeveynler için stres ve endişeye ve sağlık hizmeti sağlayıcıları için önemli bir iş yüküne neden olur. Bu çalışmanın amacı, tam kan sayımı parametrelerini kullanarak üst solunum yolu enfeksiyonu olan ateşli çocuklarda FS riskini öngörebilen faydalı belirteçleri belirlemektir.

Yöntemler: Çalışmaya 6 ay ile 5 yaş arasında, 240 ilk FS öyküsü olan, 121 nöbetsiz akut ateşli üst solunum yolu enfeksiyonu olan (AFI) ve 115 sağlıklı kontrolden oluşan toplam 476 çocuk çalışmaya dahil edildi. Çalışmaya yaş ve cinsiyet uyumlu biri nöbetsiz ateşli hastalardan ve diğeri sağlıklı çocuklardan oluşan iki kontrol grubu alındı.

Bulgular: Tüm katılımcılar birlikte değerlendirildiğinde, lojistik regresyon analizi, hemoglobin (Hb) seviyesinin ≤10,95 FS için 2,937 kat daha fazla riskle ve nötrofil/lenfosit oranı (NLR) ≥1,3969 ile 2,719 kat FS artışı ile ilişkili olduğunu ortaya koydu (%95 güven aralığı: 1,885-4,576 vs. 1,873-3,949), (p<0,001).

Sonuç: FS riskini öngörmek için düşük Hb seviyeleri ve yüksek NLR kullanılabilse de bu değerler AFI'lı çocuklarda FS'yi öngörmek için tek başına yeterli değildir.

Anahtar Kelimeler: Ateşli nöbet, öngörü, hemoglobin, nötrofil/lenfosit oranı

Introduction

Febrile seizures (FS) are the most frequent neurological problems in childhood.[1] They are most common at 12-18 months and in boys (M/F: 1.1/1-2/1).[2,3] Most cases consist of the simple FS (SFS) type, viral infections being the principal underlying cause.[4] Nutritional deficiencies such as iron deficiency, anemia, zinc deficiency, and vitamin B12 deficiency, and genetic factors also occupy an important place in the etiology of FS.[5]

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Received/Geliş Tarihi: 18.08.2021 **Accepted/Kabul Tarihi:** 07.01.2022

The febrile state is triggered by proinflammatory cytokines released during infections.[6] The most important cytokines in the development of FS are IL-1β and TNF-α.[7] These exhibit direct and indirect modulating effects on neurons and neurotoxic neurotransmitters released during excitation or inflammation.[8] Inflammation also involves the major immune system cells subtypes, including neutrophils and lymphocytes, and immune system activation is of considerable importance in patients with FS.[8]

Febrile seizures are rarely associated with significant morbidity or long-term health problems. However, they cause stress and anxiety in parents and increase healthcare providers' workloads.[9] It is therefore important to predict which children with fever will also undergo seizures.

Despite their being highly useful and important biomarkers, the accessibility of inflammatory cytokines is limited, and the costs involved are high. There is, therefore, growing interest in the use of low-cost complete blood count (CBC) inflammatory response markers for determining susceptibility to FS.[2,3,10,11]

The purpose of the present study was to identify useful markers capable of predicting the risk of FS in febrile children with upper respiratory infection using CBC parameters.

Materials and Methods

This retrospective study was conducted at the pediatric emergency department of a tertiary referral hospital in Turkey between October 2017 and October 2020. Four hundred seventy-six children aged between six months and five years, 240 with a history of first FS, 121 with acute febrile illness without seizures (AFI), and 115 healthy controls were enrolled.

The control group was recruited from two age-and-sex matched groups:

1. A healthy group was recruited from healthy children admitted to a general pediatric outpatient clinic for routine control.

2. An AFI without seizure group was recruited from children admitted to the general pediatric outpatient clinic with fever and diagnosed with an acute upper respiratory infection.

Definitions

FS were defined as seizures occurring at fever levels ≥38 °C, in children between six months and five years of age, with no previous history of afebrile seizure, and not accompanied by central nervous system infection or acute metabolic disease.[12]

Simple FS (SFS) were defined as seizures lasting less than 15 min, not recurring during 24 h or the same infectious process, and exhibiting a generalized characteristic.[7]

Complicated FS (CFS) were defined as seizures lasting ≥15 min or recurring within 24 h or in the same infectious process and exhibiting a focal characteristic.[12]

Diagnosis of anemia was based on hemoglobin (Hb) levels below 2 SD of age-matched values.[13]

Exclusion Criteria

Exclusion criteria in both the patient and control groups were: Prematurity (≤37 weeks), presence of any chronic diseases (bronchopulmonary dysplasia, neuromuscular diseases, epilepsy, congenital cardiovascular diseases, immunodeficiency, etc.), previous history of febrile and/or afebrile seizures, suspicion of meningitis, electrolyte imbalance, history of fever exceeding 48 h in duration, antibiotic use within the previous two weeks, and not being tested for CBC and C-reactive protein (CRP) blood levels.

Individuals with a fever origin other than acute upper respiratory infection in the FS and AFI groups, or with a history of any infection within the previous two weeks among healthy children were also excluded.

Study Design

Demographic characteristics including the patient's age, gender, duration and recurrence of FS episodes, family history of FS and epilepsy, parental consanguinity, and CBC and CRP values were retriev from the medical charts.

Laboratory Analysis

CBC and CRP tests were routinely performed for all children with and without FS in our hospital. These tests were performed from peripheral venous blood samples collected during hospital admission. CBC values were measured using an automatic hematology analyzer (MINDRAY BC-6800) with hydrodynamic focusing flow cytometry.

Serum CRP levels were assessed using the immunoturbimetric method (Abbott Architect-plus C8000, Diagnostic Inc., USA), values >5 mg/L being considered positive.

CBC findings including Hb, hematocrit, mean corpuscular volume (MCV), red blood cell distribution width (RDW), white blood cell count (WBC), neutrophil, and lymphocyte counts, and platelet count, values were retrieved from patients' medical records. The neutrophil to lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Ethics

Approval for the study was obtained from the Local Ethics Committee of Aydın Adnan Menderes University (decision no: 11, date: 17.01.2021). Informed consent was not obtained due to the retrospective design of the study.

Statistical Analysis

Statistical analyses were performed on SPSS 21 software (IBM Corporation, Armonk, NY, USA). Normality was assessed using the Kolmogorov-Smirnov test and descriptive statistics. Categorical variables were expressed as number and percentages. Continuous variables are expressed as mean plus standard deviations or median values and interquartile range (25 and 75 quartiles) depending on normality of distribution. Non-parametric or parametric tests were performed accordingly. Student's t-test or One-Way Analysis of Variance were used for normally distributed parameters, while quantitative variables were compared between the groups using either the Mann-Whitney U test or Student's t-test. Receiver operating curve (ROC) analysis was performed to determine CBC data cut-off values capable of predicting the development of FS. Risk analysis based on cut-off values was performed using logistic regression. P-values <0.05 were considered statistically significant.

Results

Patient Characteristics

Two hundred forty children with FS (171 SFS and 69 CFS), 121 with AFI, and 115 healthy age-and-sex matched children were included in the study.

The participants' demographic characteristics are shown in Table 1. There was no difference between the groups in terms of gender or age (p>0.05). Boys represented 57.9% of the patients. Median age at first FS was 25.42±14.95 months, and the median seizure duration was 1.86±1.49 min. Analysis showed that 71.3% of FS were simple and 28.7% complex.

A history of FS in first-degree relatives was determined in 55 (23.1%) patients, and in second-degree relatives in 20 (8.4%) (Table 1).

A comparison of laboratory parameters between children with FS, or AFI, and the healthy controls is shown in Table 2. Hb, MCV, and lymphocyte levels were lower, while RDW, WBC, neutrophil levels, and NLR were higher in children with FS compared to those with AFI and the healthy controls (p<0.05). Although CRP levels were lower in children with FS than in those with AFI, the difference was insignificant (p=0.127).

The cut-off, AUC, sensitivity, specificity, 95% confidence interval (CI) and p-values of the Hb, WBC, neutrophils, and NLR parameters for predicting FS in children with FS and AFI are shown in Table 3, while the ROC curves are presented in Figure 1.

A Hb cut-off value ≤10.95 g/dL predicted FS with 76.6% sensitivity and 34.6% specificity, a WBC value ≥9.405 with 63.8% sensitivity and 49.6% specificity, a neutrophil count ≥3.525 with 72.1% sensitivity and 48.8% specificity and NLR ≥1.3969 with 58.8% sensitivity and 52.1% specificity,

Logistic regression analysis of factors associated with risk of FS (Hb and NLR) is shown in Table 4. An Hb level ≤10.95 was associated with a 2.937 -fold increased risk of FS, and NLR ≥1.3969 with a 2.719-fold greater risk (95% CI: 1.885-4.576 vs 1.873-3.949, respectively), p<0.001).

However, when patients with fever (FS and AFI) were subjected to risk analysis based on CBC parameters, no parameter capable of increasing the risk was identified (OR: 1, p>0.05).

Table 1. Participants' demographic characteristics

Parameter	Children with FS (n=240) (mean ± SD)	Children with AFI (n=121) (mean ± SD)	Healthy children (n=115) (mean ± SD)	p-value
Age (months)	25.42±14.95	27.57±25.27	27.74±18.93	0.439*
Duration of seizure (minutes) (mean ± SD)	1.86±1.49	N/A	N/A	N/A
	n (%)	**n (%)**	**n (%)**	
Gender Male Female	 139 (57.9%) 101 (42.1%)	 67 (55.4%) 54 (44.6%)	 65 (56.5%) 50 (43.5%)	0.895
Type of seizure Simple Complex	 171 (71.3%) 69 (28.7%)	N/A	N/A	N/A
Family history of febrile seizure 1st degree relatives 2nd degree relatives	 55 (23.1%) 20 (8.4%)	N/A	N/A	N/A
Family history of epilepsy in first degree relatives	23 (9.7%)	N/A	N/A	N/A

n: Number, SD: Standard deviation, FS: Febrile seizure, AFI: Acute febrile illness, N/A: Non-applicable, Statistics: Cross tab chi score, *One-Way Analysis of Variance. Significance was set at p<0.05

Table 2. Comparison of laboratory parameters between children with FS, AFI and healthy controls

Parameter	Children with FS (n=240) (mean ± SD)	Children with AFI (n=121) (mean ± SD)	Healthy children (n=115) (mean ± SD)	p-value
Hb (g/dL)	11.31±1.01**	11.57±1.04**	11,94±0.94*	**<0.001**
Hct (%)	34.64±2.73	34.79±3.00	38.58±34.08	0.100
MCV (fl)	75.16±6.18**	77.53±5.98*	76.64±4.77	**0.001**
RDW (%)	15.03±3.27**	13.78±1.22*	13.81±1.40*	**<0.001**
WBC (10^3/mm^3)	11.98±5.407**	10.80±5.174*	10.04±3.118	**0.001**
Neuthrophils count (x10^3/mm^3)	6.866±4.792*	5.573±3.669*	3.610±1.827**	**<0.001**
Lymphocytes count (x10^3/mm^3)	3.857±2.599**	4.171±3.012**	5.201±2.075*	**<0.001**
PLT (10^9/L)	319.63±251.88	302.83±117.32	351.81±84.05	**0.139**
PCT (%)	0.267±0.106	0.254±0.095**	0.291±0.064*	**0.011**
MPV (fL)	8.871±0.94	8.49±0.79	8.54±0.84	0.051
PDW (fL)	14.05±2.45**	15.66±0.37*	15.53±0.32*	**<0.001**
NLR	2.806±3.410*	2.046±2.395*	0.866±0.780**	**<0.001**
PLR	109.79±73.92*	101.47±72.56*	77.91±34.65**	**<0.001**
MPV/PLT	0.032±0.012*	0.032±0.014*	0.026±0.008**	**<0.001**
CRP (mg/L)	15.352±25.307	19.664±25.191	-	**0.127**

Statistics: One-Way ANOVA, post-hoc test, Scheffe: (*is significantly larger than **p<0.05)
n: Number, SD: Standard deviation, FS: Febrile seizure, AFI: Acute febrile illness, Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean corpuscular volume, RDW: Red blood cell distribution width, WBC: White blood cell, PLT: Platelet, PCT: Platelet crit, MPV: Mean platelet volume, PDW: Platelet distribution width, NLR: Neuthrophil to lymphocyte ratio

Table 3. ROC curves for Hb, WBC, neutrophils and NLR to predict febrile seizure in children with FS and AFI

Variable	Cut-off value	Sensitivity	Specificity	AUC, CI%	p-value*
Hb (g/dL)	≤10.95	0.766	0.346	0.374-0.499	**0.049**
WBC (10^3/mm^3)	≥9.405	0.638	0.496	0.524-0.628	**0.040**
Neuthrophil count (x10^3/mm^3)	≥3.525	0.721	0.488	0.507-0.631	**0.032**
NLR	≥1.3969	0.588	0.521	0.508-0.631	**0.031**

Hb: Hemoglobin, WBC: White blood cell, NLR: Neuthrophil to lymphocyte ratio, FS: Febrile seizure, AFI: Acute febrile illness, CI: Confidence interval, *ROC curve analysis. Significance was set at p<0.05

Table 4. Logistic regression analysis of Hb and NLR associations

Variable	OR	95% CI	p-value	Risk
Hb (≤10.95 g/dL)	2.937	1.885-4.576	**<0.001**	+
NLR (≥1.3969)	2.719	1.873-3.949	**<0.001**	+

Hb: Hemoglobin, NLR: Neutrophil to lymphocyte ratio, OR: Odds ratio, CI: Confidence interval. Significance value was set at p<0.05

Discussion

The present research is one of the few studies in the literature investigating all CBC parameters for predicting the risk of FS in febrile children with upper respiratory infection and comparing with AFI and healthy children

Previous studies have reported inconsistent results concerning the relationship between anemia and FS in children. Daoud et al.[14] and Vaswani et al.[15] reported significantly lower mean serum ferritin levels in children with first FS than in children with AFI without seizures. Additionally, Kumari et al.[16] reported significantly lower serum ferritin levels in children with first SFS compared to children with AFI without seizures, although no significant differences were observed in mean Hb values or mean blood indices. However, Derakhshanfar et al.[17] suggested that iron can play a protective role against FS. They attributed that role to the involvement of, iron in the activity of neurotransmitters such as monoamine oxidase and aldehyde oxidase. Those authors thus concluded that iron deficiency leads to a reduction in the excitation power of neurons and thus can play a protective role against FS in anemic patients.[17] Another study evaluating the relationship between anemia and first simple FS in 240 patients aged six months to five years, observed no association between anemia and seizure.[18]

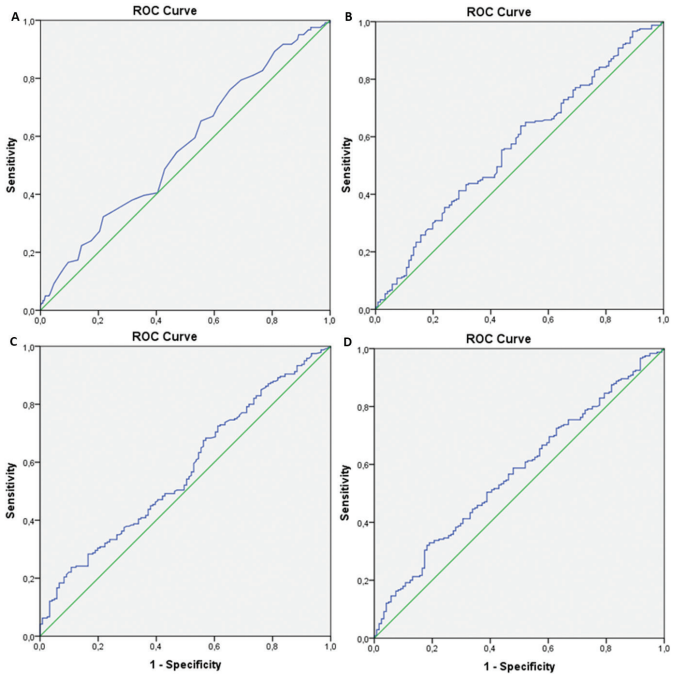

Figure 1. A: Receiver operating curve (ROC) curve for hemoglobin to predict febrile seizures (FS) in children with fever, **B:** ROC curve for white blood cell to predict FS in children with fever, **C:** ROC curve for neutrophil to predict FS in children with fever, **D:** ROC curve for neutrophil lymphocytes ratio to predict FS in children with fever

Animal studies have shown that iron deficiency affects myelination and the synthesis of neurotransmitters.[19] The first finding in the present study was lower Hb and MCV levels and higher RDW levels in children with FS compared to age-and-sex matched controls. When all the patients in the study were analyzed together, the optimal Hb cut-off value identified at ROC analysis was ≤10.95. Logistic regression analysis revealed that Hb level ≤10.95 was associated with a 2.937 -fold increased risk of FS (95% CI: 1.885-4.576).

In the light of the patients' age groups, the CBC parameters (low Hb and MCV and high RDW), and the causes of anemia, the findings of the present study suggest that anemia may derive from iron deficiency. We think that anemia developing in association with iron deficiency and fever may have made children more susceptible to seizures by reducing neuronal excitability in maturing brain cells and lowering the seizure threshold.[20]

IL-1β, one of the cytokines released during fever, stimulates cortisol secretion.[21] Cortisol in turn triggers an increase in neutrophils and leukocytes and a decrease in lymphocytes.[22] Woiciechowsky et al.[23] reported that intracerebroventricular IL-1β infusion significantly increased the numbers of peripheral neutrophils but reduced those of lymphocytes.

Gontko-Romanowska et al.[3] showed significantly higher neutrophil and significantly lower lymphocyte levels in children with FS compared to febrile children without seizures. Biyani et al.[24] concluded that increased leukocyte counts may be due to the stress caused by seizures. Similarity to Biyani et al.[24] Toyosawa[25] showed that electrically induced seizures immediately increased peripheral leukocyte counts in rabbits.

NLR is a measure of systemic inflammation.[7] Liu et al.[7] showed significantly higher NLR values in children with FS compared to febrile children without seizures. Another study of children with first seizure episodes of FS and febrile children reported higher WBC and NLR in children with FS.[20]

Another important finding in this study was that WBC, neutrophil counts and NLR were higher, while lymphocyte counts were lower in children with FS than in the control groups. Additionally, when all participants were evaluated together, the optimal WBC, neutrophil, and NLR cut-off values at ROC analysis were ≥9.405, ≥3.525, and ≥1.3969 respectively. Logistic regression analysis revealed that NLR ≥1.3969 was associated with a 2.719 -fold increased risk of FS (95% CI: 1.873-3.949).

The underlying mechanism of the relationship in FS is complex and is only gradually being elucidated. We think that the elevation in our results may not only indicate the presence of toxins in circulation as a result of an inflammatory reaction, but may also derive from a transient and rapid increase in catecholamine-derived neutrophils and leukocytes resulting from stress-induced by seizure and fever. Our CRP results (CRP was lower in children with FS than in those with AFI although the difference was not significant appear to support this idea.

CRP is an acute-phase reactant released during the course of infection and in several forms of inflammation.[26] Similarly to the findings of the present study, Yigit et al.[11] and Biyani et al.[24] observed no significant difference between groups with FS and with fever without seizure in terms of CRP levels (14.92 mg/dL vs 19.3 mg/dL and 11.67 vs 13.89, respectively). However, Gontko-Romanowska et al.[3] reported significantly lower CRP levels in children with FS compared to febrile children without seizures (15.73 vs. 58.50, respectively).

This is because viral infections are the principal underlying cause of FS and CRP elevation is not only a result of underlying infection but also of epinephrine release and demargination of neutrophils due to seizure stress. The higher CRP levels in children with AFI may be due to the inflammatory process increasing gradually to raise CRP to higher levels.[27]

Study Limitations

Due to the retrospective design of study, factors contributing to anemia, such as iron, ferritin, etc. levels, were not assessed therefore the etiology of anemia could not be determined precisely. Also causative micro-organism in upper respiratory infection was not identified.

Conclusion

Our findings suggest that low Hb levels and high NLR may be capable of use in predicting the risk of development of FS, but that these values are not by themselves sufficient for predicting FS in febrile children.

Clinicians must interpret blood tests results with care in order to predict FS in children from this age group. We think that, more advanced and extensive prospective studies including identifying the responsible micro-organism and evaluating the levels of IL-1β and TNF-α may ensure to elacuadiate underlying mechanism of FS and the inconsistant study results in the literature.

The strengths of this study included the fact that the febrile patients' group was homogeneous in terms of foci and duration of infection. Another strength is the presence of two control groups consisting of febrile and healthy children.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Local Ethics Committee of Aydın Adnan Menderes University (decision no: 11, date: 17.01.2021).

Informed Consent: Informed consent was not obtained due to the retrospective design of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.Ç., A.T., Design: E.Ç., Data Collection or Processing: E.Ç., Analysis or Interpretation: E.Ç., Ş.G., M.A., A.T., Literature Search: E.Ç., Ö.A., A.T., Writing: E.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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