North Clin Istanb 2025;12(5):611–619
doi: 10.14744/nci.2024.04903

ORIGINAL ARTICLE PEDIATRICS

Anemia, inflammation, circadian rhythm and season effects in febrile convulsions

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ABSTRACT

OBJECTIVE: Our aim in the study is to investigate circadian rhythm, season, age, gender, and hemogram parameters in children diagnosed with febrile convulsions.

METHODS: The data of a total of 478 children, consisting of 160 patients with febrile convulsions (90 male/70 female) and 318 control groups (healthy, convulsiyon free- febrile), were compared.

RESULTS: The average age of all patients was 25.7±14.7 (minimum 6-maximum 60) months, and the most common convulsion age was 13-18 months. Circadian rhythm was similar, application seasons were similar. The male/female ratio was 1.3. MPV in winter was lower than other seasons (p=0.002). At younger ages, lymphocyte count was higher (p=0.048) and NLR was lower (p=0.036). NLR was lower in patients with febrile convulsions with anemia than in patients with febrile convulsions without anemia (p=0.029). NLR was lower in patients with febrile convulsions with anemia than in the convulsion-free febrile control group with anemia (p=0.001). In patients with febrile convulsions, MPV was lower (p=0.033) and NLR was higher (p=0.001) than in the convulsion-free febrile control group. One third of the patients had hypocapnia.

CONCLUSION: Young age, anemia, inflammation, and hypocapnia may facilitate the occurrence of febrile convulsions. MPV and NLO, which are hemogram parameters, can guide us about inflammation. Blood gases may provide information regarding hypocapnia. These rapid examinations may help elucidate the etiology. Prospective studies are needed for circadian rhythm in febrile convulsions.

Keywords: Circadian rhythm; febrile convulsions; hemogram parameters; hypocapnia.

Cite this article as: *Surucu Kara I, Aydin Peker N, Arslan YK, Mertoglu C. Anemia, inflammation, circadian rhythm and season effects in febrile convulsions. North Clin Istanb 2025;12(5):611–619.*

Febrile convulsions (FC) are convulsions that occur at a body temperature above 38°C without central nervous system infection, trauma, metabolic abnormality, electrolyte imbalance, drug intake, and history of afebrile convulsions [1, 2]. FC is very common in childhood. The age of FC is between 6–60 months. It is most common around 2 years of age [2].

Body temperature is regulated by cell clusters in the hypothalamus, showing circadian rhythm variation. The body has a circadian rhythm. Thanks to the circadian rhythm, body temperature can be controlled for 24 hours [3]. The circadian rhythm develops from approximately the age of five [4]. Circadian rhythm in children is affected by internal-external factors. [3–5]. The circadian rhythm is

Received: June 05, 2023 *Revised:* September 09, 2023 *Accepted:* September 24, 2024 *Online:* November 03, 2025

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associated with many agents in the central nervous system. Melatonin is the pineal hormone. It can inhibit the central nervous system. Day-night differences in melatonin levels have been demonstrated during convulsions. The production of kynurenine pathway metabolites (proconvulsant/anticonvulsant) in convulsion is different. Arginine vasopressin modulates the thermoregulatory response, and arginine vasopressin level increases at high fever [4].

Body temperature may vary according to gender, age, outdoor temperature, metabolic rate, and time of day [3–5]. Body temperature is about 36.5 ºC in the early morning and 37.5 ºC in the evening [3]. Body temperature reaches its highest level in the afternoon [3–5]. There is a physiological increase in body temperature in the evening [4].

High fever causes changes in neuronal activity in the anterior hypothalamus, hippocampus, and cerebral cortex due to infection or non-infection reasons, and is a defense mechanism [3–5].

A one-degree increase in body temperature can cause an increase in breathing rate of 3.7 breaths per minute, which can cause a change in blood gas and a decrease in PCO_2 [5]. pH changes have a central role in the brain. pH changes control convulsion activity. It has been shown in animal (mouse) experiments that alkalosis increases neuronal excitability and facilitates epileptic activity. Hyperthermia causes hyperventilation. Intracerebral hypocapnia and alkalosis resulting from hyperventilation may cause convulsions [6, 7].

Anemia causes an energy metabolism disorder. Changes in the synaptic neurotransmitter system and delay in myelin development may occur due to anemia [8].

Fever, age and genetic predisposition, positive family history, central thermoregulation disorders, iron, and zinc deficiency, humoral immune system disorders, hyperventilation and respiratory alkalosis due to hyperthermia, changes in cytokines, daily and seasonal changes, changes in melatonin levels, and many other conditions have been investigated and associated with febrile convulsions [5–7, 9, 10]. The cause of febrile convulsions is not fully understood [3, 7].

In our study, we aimed to investigate the etiological importance of circadian rhythm, season, age, gender and hemogram parameters in children diagnosed with febrile convulsions.

Highlight key points

- Young age, anemia, inflammation, and hypocapnia appear to facilitate the development of febrile convulsions.
- MPV and NLR values may serve as quick hemogram markers reflecting inflammatory activity in febrile convulsions.
- Circadian rhythm and seasonal variation showed no significant influence on febrile convulsion occurrence.

MATERIALS AND METHODS

It is a descriptive study conducted retrospectively on patient records. The university medical sciences ethics committee gave permission for the study with the decision numbered 07/09 taken at the session numbered 07 (Ethics committee approval, date of receipt 25/06/2019). This study was conducted in accordance with the Declaration of Helsinki. It was done between 2012–2019. Patients who applied to the pediatric emergency outpatient clinic of the research hospital due to febrile convulsions were retrospectively analyzed.

Patient Group Selection

The anamnesis of the pediatric patients aged between 6 and 60 months who had a febrile convulsion was reviewed from the records of patients. Previous diagnoses, medications, radiographs, brain images and examination results were checked. Time of admission, season, age, additional diagnosis of febrile convulsion, hemogram parameters, CRP level, gender, and recurrent febrile convulsions, if any, were recorded.

Patients with severe anemia (those with Hb levels that would indicate insufficiency such as tachypnea, tachycardia), neurometabolic disease, younger than six months, older than sixty months, with central nervous system infection or inflammation, acute systemic metabolic abnormality that may cause convulsions, history of afebrile convulsions or head trauma, respiratory distress, severe diarrhea-vomiting (those with moderate to severe dehydration, those with fluid electrolyte imbalance, those with acidosis), hemodynamic disorders, who applied to the hospital long after their convulsions, and patients who had previously been diagnosed with mental-motor retardation, malignancy, or rheumatological disease were excluded from the study. The patients with complex FC, acute gastroenteritis and lower respiratory tract infections were excluded from this study.

Control Group Selection

Healthy control group: The records of patients who were brought to the control for healthy child examinations or referred by the family doctor for control were examined. Children with hemogram examination in

their files were recorded as the control group. The anamnesis of the patients in this control group was analyzed from the records. Previous diagnoses, medications, radiographs, brain images and examination results, if any, were checked, and those with a previous diagnosis of chronic or acute disease or drug use were excluded from the study.

Convulsion-free febrile control group: Patients of similar age and gender, without a diagnosis of chronic disease, only diagnosed with fever and/or fever. Children with hemogram examination in their files were recorded as the control group. The anamnesis of the patients in this control group were analyzed from the records. Previous diagnoses, medications, radiographs, brain images and examination results, if any, were checked, and those with a previous diagnosis of chronic or acute disease or drug use were excluded from the study.

Evaluation of laboratory parameters: From the hemogram parameters, white blood cell count (WBC), platelet (PLT) counts, mean platelet volume (MPV), hemoglobin (HGB), red cell distribution width (RDW), mean corpuscular volume (MCV), red blood cell (RBC) and neutrophil and lymphocyte counts were recorded. The neutrophil-to-lymphocyte ratio (NLR) was calculated. The NLR result was written by dividing the absolute neutrophil counts by the absolute lymphocyte counts. Anemia was accepted if hemoglobin was lower than 10.5 g/dL in children aged 6 months to 2 years and if hemoglobin was lower than 11.5 g/dL in children aged 2–5 years and if MCV and RBC were low for age [11]. The reference range accepted by our hospital laboratory was used. Reference ranges of hemogram parameters were WBC 4000–11000 mm^3, neutrophil 1500–8000 mm^3, lymphocytes 2000–8000 mm^3, RDW 11–14%, MPV 9–12 femtoliter (fl), PLT 150–450×10^3 ml. Reference ranges of biochemical parameters were glucose 60–100 mg/dl, sodium 135–145 mmol / L, potassium 3.5–5.1 mmol / L, calcium 8.5–10.8 mg/dl, CRP 0–5 mg / L. Reference ranges of blood gas parameters were pH 7.35–7.45, pCO_2 35–45 mmHg, HCO_3 22–26 mmol/L. Blood gases were studied in some of the patients. The patients whose blood gas was taken were also evaluated within themselves.

Evaluation of circadian rhythm: The day was divided into six-hour periods to evaluate for circadian rhythm. Between 06:00 and 12:00 was considered as morning, between 12:00 and 18:00 was considered as noon, between 18:00 and 24:00 as evening, and between 24:00 and 06:00 was considered as night. The time when the patients first applied to the outpatient clinic was recorded.

Statistical Analysis

We performed the statistical analysis using IBM SPSS 21.0 (Armonk, NY: IBM Corp.) program. We presented the results as mean±standard deviation for continuous variables, median/interquartile range for medians, and minimum-maximum n (%) for categorical variables. We confirmed the normality of the distribution in continuous variables with the Shapiro-Wilk test. We used the Student's t-test or the Mann-Whitney U test, depending on whether the statistical hypotheses were fulfilled in the comparison of independent continuous variables between the two groups. We used paired samples t-test and Wilcoxon signed-rank test when evaluating dependent continuous variables. We accepted a p-value of <0.05 as statistical significance.

RESULTS

The number of patients diagnosed with febrile convulsions in our study was 160, of which 90 (56.3%) were male and 70 (43.7%) were female. 160 healthy control groups of the same age and gender and 158 febrile control groups without convulsions of the same age and gender were also included in this study. The incidence in male was 1.3 times that of females. The mean age was 25.7±14.7 (minimum 6- maximum 60) months, and 58.1% of these patients had febrile convulsions between 6–24 months. In these, the most common age of convulsion was found to be 13–18 months. When we divided the day into 6 hours, 63 (39.4%) patients were admitted to the pediatric outpatient clinic (emergency or general outpatient clinic) at night and in the morning, and 97 (60.6%) patients were admitted afternoon and evening. The most frequent application was between 12:00–18:00. The highest number of patient admissions was in the summer months with 26.9%. Upper respiratory tract infection (94.4%) was the most common diagnosis accompanying febrile convulsions (Appendix 1).

Anemia was present in 13 of 160 patients (8.1%). Hemoglobin levels were lower in children first two years of age than those at other ages ($p<0.001$) (Appendix 1). MPV value was lower in winter ($p=0.002$) (Appendix 1). Lymphocyte levels were higher in children aged 6–12 months than in children aged 25–30/37–60 months ($p=0.048$), and NLR was higher in children aged 49–60 months than other months ($p=0.036$) (Appendix 2). Biochemical parameters were glucose: 122.5±32.2 mg/dl, sodium: 134.5±2.8 mmol/L, potassium: 4.2±0.5 mmol/L, calcium: 9.5±0.5 mg/dl. CRP was studied in 143 of 160 patients, of which 79 (49.4%) were CRP neg-

Table 1. Relationship between gender, age groups, and pH, PCO_2, HCO_3 of patients with febrile convulsion

	n	pH^+	p	pCO_2^+ (mmHg)	p	HCO_3^+ (mmol/L)	p
Total	82	7.32±0.09		38.8±9.0		19.2±2.6	
Gender							
Girls	33	7.30±0.89	0.123	40.8±7.4	0.093	19.2±2.4	0.081
Boys	49	7.33±0.10		37.4±9.8		19.1±2.7	
Age groups							
6–12 m	13	7.32±0.09	0.119	38.1/18.7 (16.7–55.1)	0.169*	18.6±2.7	0.204
13–18 m	18	7.30±0.09		41.1/11.5 (22.3–54.2)		18.8±2.1	
19–24 m	15	7.36±0.10		31.1/10 (20.4–55.6)		19.3±1.6	
25–30 m	10	7.35±0.07		36.3/11.1 (24.3–46.3)		19.9±2.4	
31–36 m	8	7.33±0.04		41.4/9.5 (34.2–49.9)		20.9±1.19	
37–48m	11	7.31±0.09		37.9/15.7 (31.9–53.6)		19.3±3.9	
49–60 m	7	7.24±0.11		42.9/17.9 (31.3–60.9)		17.4±3.4	

+: Results are presented as Mean±SD and/or Median/IQR (minimum-maximum); *: Kruskal- Wallis test. pH: Power of hydrogen; PCO_2: Partial carbon dioxide pressure; HCO_3: Bicarbonate; SD: Standard deviation; IQR: interquartile range for medians; m: Month.

ative, 38 (23.8%) had moderate CRP elevation, and 26 (16.3%) had very high CRP. The blood gas parameters of 82 patients were evaluated. The value ranges of pH, pCO_2, HCO_3 among the blood gas parameters included in the study were as follows, respectively: pH 7.30±0.09, pCO_2 38.8±9.0 mmHg, HCO_3 19.2±2.6 mmol/L. There was no relationship between gender, age groups and pH, PCO_2 and HCO_3 (Table 1). There were 46 (56.1%) patients with pH<7.35, 30 (36.6%) patients with pH=7.35–7.45, and 6 (7.3%) patients with pH>7.45. There were 29 (35.4%) patients with pCO_2<35 mmHg, 34 (41.5%) patients with pCO_2=35–45 mmHg, and 19 (23.2%) patients with pCO_2>45 mmHg. There were 70 (85.4%) patients with HCO_3<22 mmol/L, 12 (14.6%) patients with HCO_3=22–26 mmol/L, and zero patients with HCO_3>26 mmol/L.

When the hemogram parameters of the febrile convulsion patient group-the control groups were compared: There were differences between the patient (FC) groups and the control groups in terms of Hb (p=0.006), MPV (p=0.033), WBC (p=0.001), lymphocyte (p=0.001), neutrophil-lymphocyte ratio (p=0.001) (Table 2). Anemia was found in 13 (8.1%) of 160 patients, 31 (19.6%) of 158 in the convulsion-free febrile control group and 21 (13.1%) of 160 in the control group (p=0.011) (Table 3, 4).

Twenty-seven (16.9%) of 160 patients diagnosed with FC had recurrent convulsions. Of those who had recurrent convulsions, 14 (51.9%) were boys and 13 (48.1%) were girls, with a male-female patient ratio of 1.07. Eighteen (66.7%) of 27 patients had their first convulsion before the age of two and six (22.2%) before the age of one. Twenty-seven patients with recurrent convulsions had a mean convulsion recurrence rate of 2.4±1.08 and had a history of at least one recurrent convulsion and at most four recurrent convulsions.

DISCUSSION

The childhood period between six and sixty months, when febrile convulsions are seen, is the age range in which infections are most common [8, 11]. In this age group, the sensitivity and neuronal excitability of the brain tissue to a sudden increase in body temperature is high [3, 12]. 50–70% of children with FC may have convulsions in the first 24 months and most frequently in 18–24 months [2]. In our study, FC was detected in approximately half of our patients in the first 24 months, the most common age range was 13–18 months, and our study was compatible with the literature. In some studies on the circadian rhythm in the formation of febrile convulsions, it has been reported that FC is five times or seven times higher between 18:00 and 24:00 in the evening, and in some studies, body temperature is higher in the afternoon and evening [3, 4, 9, 13, 14]. It has been suggested that the circadian rhythm does not change the tendency of convulsions and that exceeding the convulsion threshold

Table 2. Hemogram parameters in the control groups and patients with febrile convulsion

	Patient+	Convulsion-free febrile control group+	Control group+	p
HGB (gr/dL)	11.9±0.9 11.9/1.1 (8.6–14.4)	11.4±1.2 11.7/1.4 (8–16.1)	12.1±1.0 12.1/1.3 (8.1–14.0)	**0.006**
RDW (%)	14.6±2.3 14.0/2.2 (11.9–32.0)	15.0±2.3 14.2/2.9 (11.7–24)	14.3±1.7 13.9/1.8 (11.4–22.0)	0.062*
MPV (fl)	8.4±1.1 8.4/1.6 (4.6–11.1)	8.8±1.2 9.0/1.8(6.1–11.5)	8.7±1.2 8.7/1.7 (6.2–11.7)	**0.033***
PLT ($\times 10^3$ ml)	323±112 302/121 (135–835)	308±125 290/134 (116–1087)	342±86 337/104 (176–683)	**0.001***
WBC (mm^3)	12611±5516 11200/6875 (2800–35700)	11715±6219 10650/8100 (1800–37500)	8693±1849 8800/2775 (4200–14500)	**0.001***
Neutrophil (mm^3)	7522±4997 6652/6093 (223–30345)	6414±4899 5675±5799 (316–31205)	2930±1499 2622/1682 (523–10686)	**0.001***
Lymphocyte (mm^3)	3684±2204 3414/2575 (88–14081)	4092±2434 3551/2744 (343–12486)	4822±1406 4690/2065 (1881–8353)	**0.001***
NLR (Neutrophil /lymphocyte)	2.9±3.0 1.9/2.4 (0.1–19.3)	2.2±2.5 1.3/1.7 (0.1–16.4)	0.7±0.6 0.5/0.5 (0.1–4.6)	**0.001***

+: Results are presented as Mean±SD and/or Median/IQR (minimum-maximum); *: Kruskal-Wallis test. HGB: Hemoglobin; red blood cell distribution width (RDW) reference range: 11–14%; mean platelet volume (MPV) reference range: 9–12; PLT: Platelet reference range: 150–450×10^3 ml; white blood cell count (WBC) reference range: 4000–11000 mm^3; neutrophil 1500–8000 mm^3; lymphocytes 2000–8000 mm^3; femtoliter (fl); SD: Standard deviation; IQR: interquartile range for medians

according to environmental or genetic sensitivity in situations that facilitate an increase in body temperature such as infection causes convulsions [9]. In our study, most of our patients came in the afternoon. But there wasn't statistical significance. This result cannot suggest that circadian rhythm may have an effect on FC formation. It has been reported in many studies that febrile convulsions occur most frequently in winter and in January, and this may be associated with a higher incidence of febrile illness in winter [4, 9, 13, 14]. In some studies, febrile convulsions were reported to be associated with seasonal viral outbreaks [15]. The prevalence of febrile convulsions was found to be high from late spring to summer [15]. For our patients, the most frequent application month was September, and the most frequent application season was summer. Frequency rates were similar in all seasons. In our study, upper respiratory tract infection was found to be the most common cause in children with FC.

Studies have also shown that patients with febrile convulsions have hyperventilation and respiratory alkalosis due to hyperthermia, and that intracerebral hypocapnia and alkalosis may cause convulsions [6, 7]. In a study comparing patients who applied to the pediatric department with fever without gastroenteritis or lower respiratory tract infection (LRTI), it was suggested that hypocapnia may be one of the main mechanisms in the onset and maintenance of febrile convulsions [10]. One-third of our patients had hypocapnia, which supports the literature.

There are studies that anemia lowers the convulsion threshold and increases the risk of FC [8, 16]. Iron participates in the structure of some enzymes in many neurotransmitter metabolism in the central nervous system. Iron deficiency anemia is common in developing countries and in children aged 6 to 24 months. Iron deficiency anemia in children with FC is reported to be more common in children than in controls. It is suggested that iron deficiency anemia facilitates the occurrence of convulsions. The iron levels of our patients could not be checked. The frequency of anemia was more common in the the convulsion-free febrile control group and in the healthy control group than in patients with febrile convulsions. In patients with febrile convulsions with anemia, RDW was higher and NLR was lower than in patients with febrile convulsions without anemia. in the with anemia in the without anemia. In the convulsion-free febrile control group RDW and NLR were higher

Table 3. Anemia and hemogram parameters in the control groups and patients with febrile convulsion

	Anemia	%	Age (months)	Hb+ (gr/dL)	RDW+ (%)	Plt+ (×10³ ml)	MPV+ (fl+)
Patient with FC n=160	Yes	8.1	22.4±12.5	10.2±0.8	17.5±4.9	329±170	8.4±0.9
			25/20.5 (6–45)	10.3/1.5 (8.6–11.4)	16.0/4.7 (13.3–32)	278/112 (187–835)	8.6/1.4 (7–10)
	No	91.9	25.9±14.9	12.0±0.8	14.4±1.8	323±107	8.4±1.2
			21/20 (6–60)	12.0/1.1 (10.3–14.4)	14.0/1.9 (11.9–21)	308/122 (135–706)	8.4/1.6 (4.6–11.7)
Convulsion free-febrile	Yes	19.6	23.5±13.7	10.0±0.9	17.0±3.0	378±190	8.3±1.5
			19/23 (6–60)	10.1/1.3 (8.0–11.5)	16.4/3.8 (13.1–24)	329/125 (186–1087)	8.3/2.4 (6.2–11.4)
control group	No	80.4	25.6±14.8	12.0±0.8	14.5±1.9	290±97	8.8±1.1
			21/22 (6–59)	12.0/1.0 (10.6–16.1)	13.8/2.2 (11.7–21.1)	271/135 (116–579)	9.0/1.6 (6.1–11.5)
n=158	Yes	13.1	18.1±11.5	10.2±0.7	14.3±1.9	344±96	8.7±1.0
			12.0/18.0 (6–47)	10.3/0.8 (8.1–11.2)	13.6/2.3 (12.3–19.6)	327/153 (211–552)	8.8/1.3 (6.7–10.8)
Healthy control group	No	86.9	26.9±14.9	12.3±0.8	14.3±1.7	342±84	8.6±1.2
			21.5/21.3 (6–60)	12.3/1.2 (10.5–14)	13.9/1.8 (11.4–22)	338/100 (176–683)	8.7/1.8 (6.2–11.2)
n=160	p	**0.011****	0.740	**0.001**	**0.001**	**0.001***	**0.044***

+: Results are presented as Mean±SD and/or Median/IQR (minimum-maximum); *: Kruskal- Wallis test; **: Pearson Chi-Square; Hb: Hemoglobin; red blood cell distribution width (RDW) reference range: 11–14%; white blood cell count (WBC) reference range: 4000–11000 mm³; platelet (PLT) reference range: 150–450×10³ ml; mean platelet volume (MPV) reference range: 9–12; femtoliter (fl); neutrophil 1500–8000 mm³; lymphocytes 2000–8000 mm³; FC: Febrile convulsion; SD: Standard deviation; IQR: interquartile range for medians

in those with anemia than in those without anemia. In the healthy control group RDW and NLR were similar in the with anemia in the without anemia. It may suggest that anemia may lower the convulsion threshold in people prone to febrile convulsions.

A link between FC and inflammation has been demonstrated [17]. Overproduction of proinflammatory cytokines (interleukin -6, interleukin-1β, tumor necrosis factor-α) during infections may lower the convulsion threshold in children [18]. Publications have shown that neutrophil counts increase and lymphocyte counts decrease in patients with FC compared to control groups [19]. In our study, neutrophil count was found similar in all groups of patients with FC (Gender, age, cause of fever, season, circadian rhythm, anemia).

Neutrophil count, lymphocyte count, MPV, PLT and RDW are inexpensive indicators that can be detected easily and quickly in inflammatory reactions [19, 20]. It has been suggested that NLR is found to be significantly higher in patients with FC than in patients without FC, and that NLR may have a synergistic effect on the formation of FC [19]. In our study, NLR, neutrophil counts were significantly higher in FC patients than in the control groups, which is consistent with the literature.

It has been reported that red blood cell distribution (RDW) is an inflammatory marker, there is more inflammation in the brain in patients with complex FC, and RDW is found to be higher than patients with simple FC [19, 20]. Approximately half of our patients had high RDW, but the RDW level was similar in patients with FC and the control group.

MPV reflects the platelet volume and the rate of platelet production in the bone marrow. It can also be used as an indicator of platelet activation and inflammation severity [21]. Activated platelets secrete a large number of substances that are an important mediator of inflammation [22]. In studies, it was shown that the platelet count was significantly lower in children with FC and the MPV was significantly higher than in the control groups without FC [19]. In our study, platelet count was lower in

Table 4. Anemia and hemogram parameters in the control groups and patients with febrile convulsion

	Anemia	%	WBC⁺ (mm^3)	Neutrophil⁺ (mm^3)	Lymphocyt⁺ (mm^3)	NLR⁺
Patient with FC n=160	Yes	8.1	10992±4297	5724±3474	4259±1642	1.6±1.3
			10500/7100 (5600–20300)	4437/4600 (1713–14210)	4146/2542 (1498–7455)	1.0/1.2 (0.5–5.6)
	No	91.9	12754±5600	7681±5088	3634±2244	3.0±3.0
			11500/6900 (2800–35700)	6825/6227 (223–30345)	3336/2761 (88–14081)	2.0/2.7 (0.1–19.3)
Convulsion free-febrile control group n=158	Yes	19.6	15277±7823	9262±7003	4324±2580	3.5±4.0
			14400/9800 (5100–37300)	7761/9428 (651–31205)	3640/2644 (525–12322)	1.9/1.3 (0.1–16.3)
	No	80.4	10846±5453	5719±3969	4036±2404	1.8±1.8
			10100/7600 (1800–25500)	5289/5653(316–19933)	3484/2762 (343–12486)	1.2/1.5 (0.1–11.9)
Healthy control group n=160	Yes	13.1	8152±1752	2643±850	4524±1510	0.6±0.5
			7400/2800 (4900–10700)	2781/1418 (1332–4388)	4577/3055 (2183–7158)	0.5/0.3 (0.3–2.0)
	No	86.9	8775±1856	2973±1572	4867±1390	0.7±0.6
			8900/2700 (4200–14500)	2602/1824 (523–10686)	4747/2014 (1881–8353)	0.5/0.5 (0.1–4.7)
	p	**0.011****	**0.001***	**0.001***	**0.001***	**0.001**

+: Results are presented as Mean±SD and/or Median/IQR (minimum-maximum); *: Kruskal- Wallis test, **: Pearson Chi-Square; White blood cell count (WBC) reference range: 4000–11000 mm^3; neutrophil 1500–8000 mm^3; lymphocytes 2000–8000 mm^3; NLR: Neutrophil lymphocyte ratio; FC: Febrile convulsion; SD: Standard deviation; IQR: interquartile range for medians

patients with FC compared to the control group, but unlike other studies, MPV was statistically lower than the control group.

CRP is one of the important indicators of inflammation. CRP reaches peak values 24–48 hours after inflammatory events. Because inflammatory events progress very rapidly in FC, FC occurs before CRP reaches high values. Therefore, CRP was found to be lower in children with FC than in children without FC [23]. In our patients, CRP was mostly negative or not very high, which is consistent with the literature.

CRP is one of the important indicators of inflammation. CRP reaches peak values 24–48 hours after inflammatory events. Because inflammatory events progress very rapidly in FC, FC occurs before CRP reaches high values. Therefore, CRP was found to be lower in children with FC than in children without FC [23]. In our patients, CRP was mostly negative or not very high, which is consistent with the literature.

Children with FC may have mild electrolyte disturbances and slightly low serum sodium levels [24]. In febrile convulsions, blood glucose levels may rise temporarily as a result of acute stress-induced elevation of catecholamines, cortisol, and glucagon [25]. Electrolyte values of our patients were normal in our study, since those with electrolyte disorders that could cause convulsions were excluded from our study.

FC is slightly more common in boys than in girls. There are studies in Turkey with a male/female ratio of 1.36:1 to 1.01:1 [2]. In our study, the M/F ratio was found to be 1.3 and was consistent with the literature. Febrile convulsions may recur especially in the first two years of life (15–70%) [17, 26]. Due to the decreasing convulsion threshold with age, the probability of recurrence is high in patients younger than one year of age [17]. Family history, genetic factors, and environmental factors are risk factors for recurrence. Recurrence is more common in boys [17, 26]. There was no family history, genetic result or environmental factor in the patients' emergency clinic files. Therefore, no information could be provided on this subject. Recurrence was seen in 16.9% of our patients, in accordance with the literature, Patients with recurrence were similar in age and gender.

CONCLUSION

Young age, anemia, hypocapnia and inflammation were important in febrile convulsion. The combination of young age, inflammation and anemia may facilitate the occurrence of convulsions in children with fever. In FC patients, increased NLR and decreased platelet, decreased MPV, increased lymphocyte counts, neutrophil counts and WBC counts levels are important indicators of inflammation. In patients with FC, ıt was observed that the lymphocyte level was high and MPV was low in the winter season. It was observed that the lymphocyte count was higher and the NLR rate was lower in anemic children with febrile convulsions at younger ages. In FC, NLR and neutrophil count were higher and MPV was lower than in the control group. This situation may support that inflammatory conditions facilitate the formation of febrile convulsions. Anemia may lead to febrile convulsion even at low NLR in children with a predisposition to febrile convulsion. We did not find seasonal and circadian rhythm differences in our study. More prospective studies are needed to elucidate these issues.

Evaluation of multiple parameters such as circadian rhythm, low hemoglobin levels and inflammation parameters, blood gas parameters to elucidate the etiology of febrile convulsions are the strengths of the study. The limitations of this study are that it is a retrospective and single-center study.

Ethics Committee Approval: The Erzincan Binali Yıldırım University Clinical Research Ethics Committee granted approval for this study (date: 25.06/2019, number: 07/09).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors declared that they have no conflict of interest.

Financial Disclosure: The authors declared that no support was received from any person or institution for the study.

Use of AI for Writing Assistance: The author declared that artificial intelligence-supported technologies were not used in this study.

Authorship Contributions: Concept – ISK, NAP; Design – ISK, NAP; Supervision – ISK, CM; Data collection and/or processing – ISK, NAP, CM; Analysis and/or interpretation – ISK, YKA; Literature review – ISK, NAP, CM; Writing – ISK; Critical review – ISK, CM.

Acknowledgments: We would like to thank our patients and their mothers who participated in our study. I would like to thank all my colleagues who supported our work.

Peer-review: Externally peer-reviewed.

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Appendix 1. Relationship between gender, cause of fever, age groups, season, circadian rhythm and hemoglobin, red blood cell distribution, mean platelet volume, platelet of patients with febrile convulsion

	n	%	Age+ (months)	p	Hb+ (gr/dL)	p	RDW+ (%)	p	Plt+ (×10³ ml)	p	MPV+ (fl+)	p
Total	160	100	25.7±14.7		11.9±0.9		14.6±2.3		323/120 (135–835)		8.4±1.1	
Gender												
Girls	70	43.7	21/20 (6–60)	0.695	11.8±1.0	0.303	14.5±1.6	0.428	309/149 (135–835)	0.216*	8.4±1.1	0.486
Boys	90	56.3	21/21 (6–60)		12.0±0.9		14.8±2.7		289/111 (139–561)		8.3±1.2	
Age groups												
6–12 m	29	18.1	10.1 ±1.9	**0.001**	11.3±0.9	**0.001**	14.8±2.1	0.402	316/227 (187–835)	0.180*	8.1±1.1	0.546
13–18 m	39	24.4	15.4±1.7		11.6±1.1		15.1±3.4		320/99 (139–577)		8.5±1.2	
19–24 m	25	15.6	21.1±1.6		11.9±0.6		14.4±1.8		323/143 (135–453)		8.1±1.2	
25–30 m	20	12.5	27.8±1.8		12.3±1.1		15.1±1.9		299/106 (168–537)		8.2±1.1	
31–36 m	11	6.9	33.9±1.7		12.0±0.8		14.7±1.5		261/129 (145–433)		8.8±1.1	
37– 48 m	19	11.9	42.6±3.8		12.0±0.5		14.5±1.9		308/147 (164–488)		8.4±0.9	
49–60 m	17	10.6	55.8±4.6		12.8±0.6		13.5±1.0		262/47 (193–518)		8.4±1.2	
Cause of fever												
URTI	151	94.4	21/21 (6–60)	0.346*	11.9±0.9	0.275	14.7±2.3	0.261	306/122 (132–835)	0.736	8.4±1.1	0.318
Other	9	5.6	24/39 (6–60)		12.2±1.2		13.8±1.3		289/110 (162–509)		8.0±1.4	
Season												
Winter	40	25.0	20/28 (6–60)	0.232	12.0±1.1	0.285	14.5±3.1	0.374	313/146 (139–537)	0.720	7.8±1.0 6	**0.002**
Spring	41	25.6	18/14 (8–60)		11.9±0.8		15.1±1.7		316/123 (168–706)		8.7±1.16*	
Summer	43	26.9	24/24 (6–60)		11.6±0.9		14.7±1.9		278/140 (135–835)		8.6±1.0 6*	
Autumn	36	22.5	24/25 (9–60)		12.1±0.9		14.2±2.2		300/124 (193–561)		8.2±1.2	
Circadian rhythm												
Morning	35	22.9	29/31 (8–60)	0.231*	12.0±0.9	0.292	14.8±2.2	0.781	308/135 (148–835)	0.615*	8.4±1.0	0.978
Afternoon	52	32.8	19/19 (6–60)		11.9±1.0		14.8±3.0		310/127 (145–706)		8.4±1.0	
Evening	45	28.1	21/25 (6–60)		12.0±0.9		14.4±1.5		286/142(135–675)		8.3±1.2	
Night	28	16.1	18/10 (12–60)		11.6±1.0		14.3±2.1		297/111 (181–538)		8.4±1.3	
Anemia												
Yes	13	8.1	25/21 (6–45)	0.409	12.0±0.97	**0.001**	17.5±4.88	**0.001**	278/112 (187–835)	0.849	8.3±1.1	0.797
No	147	91.9	21/20 (6–60)		10.0±0.87*		14.5±1.88*		308/122 (135–706)		8.4±0.9	

+: Results are presented as Mean±SD, Median/ IQR (minimum-maximum); *: Kruskal- Wallis test; Hb: Hemoglobin; RDW: Red blood cell distribution width; Plt: Platelet; MPV: Mean platelet volume; fl: Femtoliter; m: Months; URTI: Upper Respiratory Tract Infection; IQR: interquartile range for medians.

Appendix 2. Relationship between gender, cause of fever, age groups, season, circadian rhythm and WBC, neutrophil, lymphocyte, neutrophil-lymphocyte ratio of patients with febrile convulsion

	n	WBC+ (mm^3)	p	Neutrophil+ (mm^3)	p	Lymphocyt+ (mm^3)	p	NLR+	p
Total	160	11200/6875 (2800–35700)		6652/6093 (223–30345)		3414/2575 (88–14081)		1.9/2.4 (0.1–19.3)	
Gender									
Girls	70	10900/6325 (2800–29100)	0.102	6457/5867 (418–22756)	0.182	3334/2723 (683–14081)	0.399	1.9/2.4 (0.1–9.5)	0.518
Boys	90	12600/7225 (2900–35700)		6968/6282 (223–30345)		3662/2672 (88–13855)		1.8/2.6 (0.2–19.3)	
Age groups									
6–12 m	29	11800/6100 (6000–22000)	0.984	6630/6198 (1092–13690)	0.439	4171/3166 (337–14081)	**0.048***	1.3/2.1 (0.2–19.3)	**0.036***
13–18 m	39	11200/6800 (4800–28600)		5720/4644 (223–23428)		3744/2890 (456–7117)		1.6/1.4 (0.2–7.5)	
19–24 m	25	10500/7445 (5700–29100)		6349/4316 (1827–22756)		3225/2202 (1113–13855)		1.8/3.7 (0.2–7.3)	
25–30 m	20	13500/8025 (3500–25300)		7417/7761 (418–20872)		3178/2303 (875–8840)		2.5/2.2 (0.1–6.7)	
31–36 m	11	13500/10410 (2800–26900)		6674/10908 (1276–18991)		3902/3876 (1086–8245)		1.6/2.2 (0.9–4.4)	
37–48m	19	11000/5000 (5000–35700)		8040/5325 (2545–30345)		2786/2468 (88–6400)		2.7/3.5 (0.4–10.6)	
49–60 m	17	14000/7450 (5100–25600)		9010/8953 (2458–24704)		1872/2592 (128–8540)		3.2/8.1 (0.4–19.3)	
Cause of fever									
URTI	151	11200/6790 (2800–35700)	0.137*	6630/5831 (418–30345)	0.981*	3483/2404 (88–14081)	**0.026***	1.8/2.4 (0.1–19.3)	**0.240***
Other	9	9400/7350 (4300–18800)		7325/10196 (223–16111)		1272/2331 (456–6249)		2.5/9.3 (0.5–19.2)	
Season									
Winter	40	10900/6725 (5000–35700)	0.601	5711/6582 (418–30345)	0.783	3224/2771 (710–10191)	0.940	1.9/3.7 (0.1–19.2)	0.749

Appendix 2 (cont.). Relationship between gender, cause of fever, age groups, season, circadian rhythm and WBC, neutrophil, lymphocyte, neutrophil-lymphocyte ratio of patients with febrile convulsion

	n	WBC+ (mm^3)	p	Neutrophil+ (mm^3)	p	Lymphocyt+ (mm^3)	p	NLR+	p
Spring	43	12200/7350 (3500–29100)		7626/5436 (223–22756)		3586/2771 (456–7480)		1.9/2.2 (0.2–12.1)	
Summer	41	11000/5700 (2800–21900)		6825/6036 (1092–16111)		3476/2764 (88–14081)		2.0/3.1 (0.2–10.6)	
Autumn	36	11000/7075 (5600–26900)		5740/7098 (1713–24704)		3710/2241 (128–13855)		1.7/2.5 (0.2–19.3)	
Circadian rhythm									
Morning	35	12300/6800 (5100–25300)	0.837	7539/6111 (1092–20872)	0.088	3224/3142 (88–8540)	0.466	2.5/3.7 (0.2–12.1)	0.202
Afternoon	52	11050/6475 (2800–28600)		5789/6889 (223–23652)		3432/3525 (456–14081)		1.7/2.4 (0.2–7.5)	
Evening	45	12200/7250 (5000–35700)		6844/6293 (418–30345)		3476/2373 (128–10191)		2.1–2.9 (0.1–19.3)	
Night	28	10450/7222 (5600–22000)		5644/4671 (1193–16111)		3720/2443 (1116–6780)		1.4/1.5 (0.2–9.5)	
Anemia									
Yes	13	10500/7100 (5600/20300)	0.271	4437/4600 (1713–14210)	0.177	4146/2542 (1498–7455)	0.328	1.0/1.2 (0.46–5.6)	**0.029***
No	147	11500/6900 (2800–35700)		6825/6227 (223–30121)		3336/2761 (88–14081)		2.0/2.7 (0.1–19.3)	

+: Results are presented as Median/ IQR (minimum-maximum); *: Kruskal-Wallis test; 1>1*. WBC: White blood cell count; NLR:Neutrophil-lymphocyte ratio; m: Months; URTI: Upper Respiratory Tract Infection; IQR: Interquartile range for medians