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Evaluation of laboratory parameters in febrile seizure types

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Abstract

Background & Objectives: Febrile seizures (FS) are the most common neurological emergencies in childhood. The differentiation of FS types is generally evaluated based on the clinical features of the seizure, and there is currently no laboratory test to guide this process. In this study, the relationship between FS types and laboratory tests was examined and the power of these parameters in differential diagnosis was investigated.*Methods:* In this retrospective study, a total of 184 cases were evaluated in three groups: simple FS (n:107), complicated FS (n:35), and control group (n:42). At the time of admission; hemogram, biochemical and blood gas analysis, prolactin, cortisol values, and laboratory indices were examined in terms of diagnosis.*Results:* Among the groups; sodium (Na), glucose (G), Glucose/potassium ratio (GPR), C-reactive protein (CRP), white blood cells (WBC), platelet count (PLT), neutrophil count (N), neutrophil/lymphocyte ratio (NLR), lymphocyte count (L), mean platelet volume (MPV), MPV/PLT ratio (MPR), Hb, Htc, lactate, prolactin, and cortisol have a statistically significant difference in values ($p<0,05$). If the simple FS and complicated FS groups were compared, a statistically significant difference was found between sodium, GPR, NLR, MPR, lactate, prolactin, and cortisol values ($p<0.001$). In the ROC curve analysis, it was determined that there was the good and excellent diagnostic ability for these parameters.
*Conclusion:*This study is one of the few studies investigating the relationship between FS types and laboratory parameters. We think that sodium, GPR, NLR, MPR, lactate, prolactin, and cortisol levels will help to differentiate FS types.

*Keywords:*Simple febrile seizure, complicated febrile seizure, laboratory values

INTRODUCTION

Febrile seizure (FS) is the most common neurological emergency in children aged 6 months to 5 years, developed due to fever without central nervous system infection, affecting approximately 2-4% of children under the age of five.[1] FS are divided into two categories, simple and complicated, according to clinical features. Simple FS is defined as self-limiting seizures with a good prognosis, and complicated FS are considered to have a higher risk for recurrence.[2]

It has been reported that many genetic and environmental factors may play a role in the pathophysiology of FS.[2] The diagnosis is usually made by history and physical examination, and there is no consensus on the importance of laboratory tests in the differential diagnosis.[3] Inflammation and the role of inflammatory mediators in the mechanisms of FS are emphasized in the literature.[2] Studies of the sensitivity and specificity of common inflammatory biomarkers such as leukocytes, neutrophils, lymphocytes, and monocyte counts have provided little evidence in this regard. However, inflammatory indices such as neutrophil/lymphocyte ratio (NLR), platelet (PLT), neutrophil/platelet ratio (NPR), mean platelet volume (MPV), and red cell distribution width (RDW) seem to be useful biomarkers at this point. In addition, the evaluation of these indices is easier and cheaper than cytokines in clinical practice.[4] Although MPV is a new indicator of inflammation, it is thought that the MPV/platelet ratio (MPR) may be more clinically significant.[5]

Prolactin (PRL) is a polypeptide secreted by lactotrophic cells of the anterior pituitary gland. In seizure, it stimulates the hypothalamic-pituitary

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axis, increases the secretion of PRL-releasing hormone in the hypothalamus, and causes the pituitary to secrete PRL, resulting in a transient increase in serum PRL levels. Routine evaluation of prolactin measurement as a diagnostic test for epileptic seizures is not recommended, however prolactin level may be useful in differentiating generalized tonic-clonic and focal seizures from psychogenic non-epileptic seizures in adults and older children.[6] In addition, during stress, there is an increase in cortisol secretion through the hypothalamus-anterior pituitary system. Changes in cortisol concentration affect many important homeostatic processes in the body, including the balance between neuron excitability and inhibition.[7,8]

Stress hyperglycemia is defined as transient high blood glucose levels that resolve spontaneously after the acute illness subsides.[9] Stress hyperglycemia and hyperlactatemia in children with severe acute illness or febrile seizures are often referred as markers for stress severity and poor outcome.[10]

Many laboratory analyzes are performed in the emergency admissions of FS patients.However, there are few studies investigating the relationship between FS and laboratory parameters. In the current study, it is aimed to evaluate the laboratory parameters of patients with simple and complicated FS and determine the importance of the results in the differential diagnosis of FS and compare them with the literature.

METHODS

The medical records of the patients who was admitted to the pediatric emergency department with complaints of fever and seizures between 2019 and 2020 were assessed, and a total of 142 patients with FSwere enrolled. Of these 142 patients,107 of them hadadmitted with simple FS, and 35 with complicated FS.

Patient selection

FS was defined as a seizure associated with a fever greater than 38°C, in a child older than six months and less than five years of age, at the absence of central nervous system (CNS) infection or inflammation, acute systemic metabolic abnormality which may cause seizures, and also at the absence of afebrile seizures history.[11]

Generalized seizures lasting less than 15 minutes and not recurring within 24 hours were considered as simple FS.[12] Seizures with focal onset, lasting longer than 15 minutes, or recurring more than once in 24 hours were considered as complicated FS.[13] The patients with a recent intravenous fluid therapy, growth retardation, chronic disease (such as immunodeficiency, kidney, cardiac, lung diseases), malabsorption, acute gastroenteritis, history of severe vomiting, CNS infection, trauma, history of afebrile seizures, status epilepticus also the patients who were admitted to another hospital, had a history of premature birth, and a family history of genetic and neurological diseases were excluded from the study. The diagnosis of FS was determined according to the International Statistical Classification of Diseases (ICD-10) codes. The patient's gender, age, seizure type, number of seizures, and laboratory results at the time of the first admission were recorded.

Laboratory

Hemogram, biochemistry, and hormone parameters measured from the first peripheral blood were evaluated. White blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), mean erythrocyte volume (MCV), hematocrit (Hct), PLT, MPV, NLR, and MPR were recorded in the whole blood count.Sodium (Na), potassium (P), calcium (Ca), glucose (G), glucose/potassium ratio (GPR), liver function tests, urea, and creatinine results were recorded in the biochemical evaluation.Ionized calcium and lactate were measured in blood gas tests. Prolactin and cortisol values were recorded from hormone tests. NLR was calculated by dividing the neutrophil count to the lymphocyte count, and MPR was calculated by dividing the MPV to the PLT count.

Blood gas analyzes were performed with the electrochemical biosensor method (ABL80FLEX-BASIC, FRANCE), whole blood count evaluations with the electrical impedance + optical scatter method (Beckman Coulter, USA), hormone examinations with the electrochemiluminescence Immunoassay (Roche Cobas E-601, USA), and clinical chemistry examinations with spectrophotometric (Abbott) 16000, USA) method.

A serum Na measured on admission below 135 mEq/L was defined as hyponatremia.[14]

Statistical methods

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data, and mean and standard deviation for continuous data were given as descriptive values. "ANOVA Test" was used for comparisons between groups, and "Chi-square or Fisher's Exact Test" was used for comparison of categorical variables. Post-Hoc Tukey test was performed to determine which groups caused the significant difference in the variables that showed a significant difference as a result of the Anova test. ROC analysis was performed and the ROC curve was drawn for the parameters thought to have a distinctive effect on the development of complicated FS and FS in general. A p value of less than 0.05 was considered statistically significant.

Ethics statement

Approval for this study was obtained from the Clinical Research Ethics Committee of Diyarbakır SBU Gazi Yaşargil Training and Research Hospital (15.01.2021/637).

RESULTS

A total of 184 cases, 142 patients with FS and 42 children in the control group were evaluated. Of the patients , 62.5% (n:115) were male and 37.5% (n:69) were female, and there was no significant difference in terms of gender. The mean age on admission was 24 months, there was no statistically significant difference between the groups. The demographic and clinical findings are given in Table 1.

Mean degree of fever in simple FS and complicated FS groups was 39.07±0.67°C, 39.39±0.75°C (p=0.019) respectively. All seizures were generalized tonic-clonic seizures. The rate of more than two seizures in the complicated FS group was 80% (n:28) while this rate was 31.8% (n:34) in the simple FS group. When the history of the patients is evaluated; regardless of seizure type, the frequency of previous seizures and Na, G, GPR, creatinine, CRP, WBC, PLT, N, NLR, L, MPR, MPV, Hb, Htc, lactate, prolactin, and cortisol values were found to be statistically significant (p<0,05).

Table 2 shows the ROC curve results to evaluate the differential effect of Na, GPR, NLR, MPR, lactate, prolactin, and cortisol values on FS. The cut-off value for the Na (AUC:0.962; 95%CI:0.939-0.985; p<0.001) was determined as ≤135.For other parameters, the area under the curve and the limit values are as follows; for GPR (AUC:0.985; 95%CI:0.968-1.000; Cut-off:>24.09; p<0.001), for NLR (AUC:0.805; 95%CI:0.716-0.894; Cut-off:>1.37; p<0.001), for MPR (AUC:0.904; 95%CI:0.846-0.961; Cut-off:>0.023; p<0.001), for lactate (AUC:0.959; 95%CI:0.928-0.990; Cut-off:>1.4; p<0.001), for prolactin (AUC:0.987; 95%CI:0.972-1.000; Cut-off:>15.11; p<0.001), for cortisol (AUC:0.976; 95%CI:0.952-1.000; Cut-off:>17.5; p<0.001). In our study, the values established for all parameters were found to have good (80-90%) and excellent (>90%) discrimination ability (Figure 1).

Table 3 shows the ROC curve results to assess the differential effect of Na, GPR, NLR, MPR, lactate, prolactin, and cortisol values on patients with complicated FS. It was determined that for the sodium value (AUC:0.914; 95%CI:0.860-0.967; Cut-off:≤130; p<0.001). For other parameters respectively, for GPR (AUC:0.966; 95%CI:0.929-1,000; Cut-off:>37.72; p<0.001), for NLR (AUC:0.918; 95%CI:0.872-0.964; Cut-off:>2.84; p<0.001), for MPR (AUC:0.960; 95%CI:0.925-0.994; Cut-off:>0.033; p<0.001), for lactate (AUC:0.882; 95%CI:0.801-0.964; Cut-off:> 3.1; p<0.001) for prolactin (AUC:0.976; 95%CI:0.949-1,000; Cut-off:>39.1; p<0.001), for cortisol (AUC:0.830; 95%CI:0.742-0.917; Cut-off:>38.4; p<0.001) was calculated. The values determined for all parameters were found to have good (80-90%) and excellent (>90%) discrimination ability (Figure 2)

DİSCUSSİON

Febrile seizures are the most common neurological disorder in children. Various laboratory tests are usually get done for these patients in pediatric emergency services.[11] Serum electrolytes, biochemical parameters, and whole blood count are the most important tests. In this study, a statistically significant difference was found in simple and complicated FS groups in terms of Na, GPR, NLR, MPR, lactate, prolactin, and cortisol levels.

Simple FS lasts less than 15 minutes and does not occur again in 24 hours. The most common seizure type is generalized tonic-clonic.[12] All of the seizures in our study were seen as generalized tonic-clonic pattern.

Yigit *et al*.[15] examined 142 patients with first FS in two groups and found the difference in mean NLR for simple and complex seizure groups to be statistically significant. In our study, we found that the NLR value was higher in patients with complicated FS.

Liu *et al*.[5] reported that the mean MPR levels were significantly higher in the FS group compared to the control group, but there was no

Table 1: Distribution of demographic and clinical findings of the participants

Characteristics	Total (N=184)	Control (n=42)	Simple FS (n=107)	Complicated FS (n=35)	p	Difference*
	n (%) or mean±SS	n (%) or mean±SS	n (%) or mean±SS	n (%) or mean±SS		
Age, month	24±14	25±16	23±13	25±14	0.646	
Fever (^{0}C)	**39.15±0.7**	NA	**39.07±0.67**	**39.39±0.75**	**0.019**	
Gender					0.132	
Female	69 (37.5)	18 (42.9)	43 (40.2)	8 (22.9)		
Male	115 (62.5)	24 (57.1)	64 (59.8)	27 (77.1)		
Number of seizures					**<0.001**	
1	**80 (56.3)**	NA	**73 (68.2)**	**7 (20)**		
2 or more	**62 (43.7)**	NA	**34 (31.8)**	**28 (80)**		
Sodium (mmol/L)	**133.41±3.84**	**138.02±1.52**	**133.2±2.37**	**128.51±2.83**	<0.001	a-b-c
Glucose (mg/dL)	**125.03±29.36**	**89.43±10.29**	**124.34±15.04**	**169.83±13.15**	**<0.001**	a-b-c
Potassium (mmol/L)	**4.39±0.35**	**4.7±0.2**	**4.4±0.27**	**4±0.31**	**<0.001**	a-b-c
GPR	**29.04±8.77**	**19.01±2.28**	**28.43±3.99**	**42.93±5.85**	**<0.001**	a-b-c
AST (U/L)	30.26±8.18	30.15±6.44	29.99±8.79	31.21±8.28	0.746	
ALT (U/L)	14.66±5.88	15.94±5.61	14.61±6.35	13.27±4.32	0.138	
Calcium (mg/dL)	9.59±0.53	9.69±0.6	9.56±0.48	9.55±0.58	0.355	
Urea (mg/dL)	21.97±6.46	22.07±6.34	21.98±6.64	21.8±6.25	0.983	
Creatinine (mg/dL)	**0.4±0.09**	**0.37±0.07**	**0.41±0.09**	**0.42±0.09**	**0.034**	a-c
CRP (mg/L)	**13.17±19.99**	**0.58±0.68**	**16.49±20.45**	**18.13±24.28**	**<0.001**	a-b, a-c
WBC (10^3/mm^3)	**12.21±5.02**	**9.3±1.94**	**12.62±5.1**	**14.44±5.82**	**<0.001**	a-b, a-c
PLT (10^3/mm^3)	**319.07±67.38**	**386±84.47**	**317.32±35.04**	**244.11±26**	**<0.001**	a-b-c
Neutrophil count (10^3/mm^3)	**6.99±3.66**	**3.92±1.49**	**7.16±3.25**	**10.16±3.79**	**<0.001**	a-b-c
NLR	**2.31±1.84**	**1.5±1.83**	**1.96±1.19**	**4.34±2.09**	**<0.001**	a-c, b-c
Lymphocyte count (10^3/mm^3)	**3.9±2.03**	**4.14±1.89**	**4.21±2.13**	**2.65±1.3**	**<0.001**	a-c, b-c
MCV (fL)	76.58±5.16	77.62±4.09	76.17±5.49	76.58±5.24	0.304	
MPR	**0.03±0.01**	**0.02±0**	**0.03±0**	**0.04±0**	**<0.001**	a-b-c
MPV (fL)	**8.51±0.79**	**7.72±0.67**	**8.55±0.6**	**9.33±0.46**	**<0.001**	a-b-c
Hemoglobin (g/dL)	**11.61±0.89**	**11.99±0.88**	**11.42±0.84**	**11.71±0.9**	**0.001**	a-b
Hematocrit (%)	**34.95±2.66**	**36.03±2.62**	**34.41±2.6**	**35.31±2.46**	**0.002**	a-b
Erythrocyte (M/μL)	4.75±1.66	4.61±0.42	4.83±2.15	4.65±0.38	0.721	
Ca^{++} (mmol/L)	1.25±0.07	1.26±0.08	1.24±0.07	1.23±0.06	0.144	
Lactate (mmol/L)	**2.33±1.06**	**1.21±0.23**	**2.29±0.66**	**3.78±0.96**	**<0.001**	a-b-c
Prolactin (μg/L)	**26.5±14.92**	**9.01±2.93**	25.72±7.98	**49.9±6.76**	**<0.001**	a-b-c
Cortisol (μg/dL)	**27.79±12.37**	**11.73±2.92**	**29.59±7.99**	**41.52±9.55**	**<0.001**	a-b-c

GPR: Glucose/potassium ratio, AST: Aspartat transaminaz, ALT: Alanin aminotransferaz, CRP: C-reactive protein, WBC: White blood cells, NLR: Neutrophil/lymphocyte ratio, MCV: Mean erythrocyte volume, MPV: Mean platelet volume, MPR: MPV/PLT ratio, PLT: Platelet count *a= Kontrol, b= simple FS, c= complicated FS

Table 2: ROC analysis result regarding the development of febrile seizure

Risk Factor	AUC (95% CI)	Cut-off	p-value	Sensitivity (%)	Specificity (%)
Sodium	0.962 (0.939-0.985)	≤135.0	<0.001	88.7	97.6
GPR	0.985 (0.968-1.000)	>24.09	<0.001	94.4	100.0
NLR	0.805 (0.716-0.894)	>1.37	<0.001	80.3	76.2
MPR	0.904 (0.846-0.961)	>0.023	<0.001	87.3	83.3
Lactate	0.959 (0.928-0.990)	>1.4	<0.001	93.0	92.9
Prolactin	0.987 (0.972-1.000)	>15.11	<0.001	95.1	100.0
Cortisol	0.976 (0.952-1.000)	>17.5	<0.001	96.5	100.0

GPR: Glucose/potassium ratio, NLR: Neutrophil/lymphocyte ratio, MPR: MPV/PLT ratio, AUC: Area under curve, Data were presented with St_β and 95% confidence interval; St_β: standard regression coefficient

statistically significant difference in the MPR value in differentiating simple and complicated FS. However, in our study, we found a significant difference between FS types in terms of MPR value. We established that MPR cut-off value >0.033 may be one of the indicators of complicated seizures.

It is stated that hyponatremia may occur due to inappropriate secretions of arginine vasopressin in acute febrile diseases.[16] In literature, it was important to measure serum sodium in a child with FS; it was stated that the lower the serum sodium, the higher the probability of recurrence of the seizure.[17] Electrolyte imbalances in febrile patients with a history of seizures may increase the risk of having seizures. In current study, significant sodium depletion was found in the FS group, especially in the complicated FS group, compared to control group. However, Navaeifar *et al*.[14] found no significant difference between simple and complicated febrile seizures in terms of mean sodium levels in their study with 248 patients.

In addition, Nickavar *et al*.[18] reported that, serum sodium and calcium concentrations were significantly lower in the FS and recurrent FS groups compared to the control group. However, there was no significant difference in serum sodium levels between FS and recurrent FS groups. Conversely, in our patient group, we determined that the frequency of previous seizures and low Na value may be related.

Although the pathogenic mechanisms of FS remain unclear, experimental studies show that inflammation and inflammatory mediators are among the main causes of FS.[4] Measurement

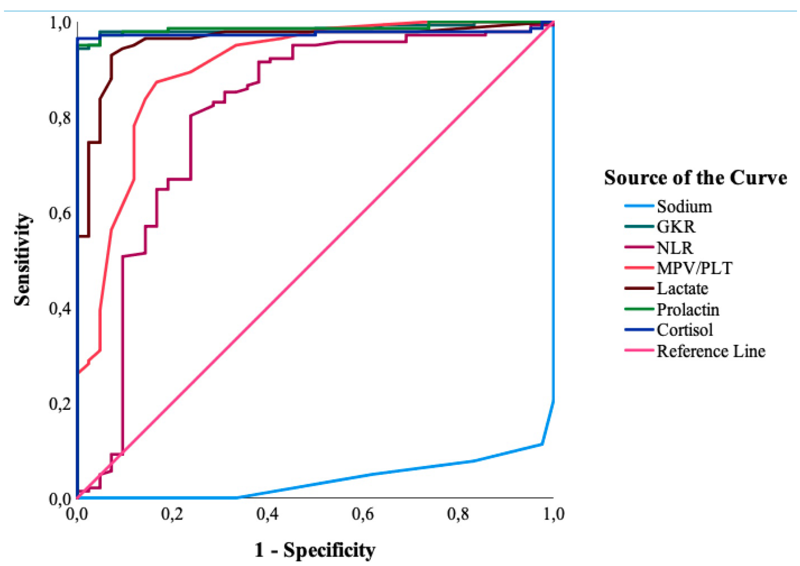

Figure 1. ROC Curve for febrile seizure development

Table 3: ROC analysis result regarding the development of complicated febrile seizure

Risk Factor	AUC (95% CI)	Cut-off	p-value	Sensitivity (%)	Specificity (%)
Sodium	0.914 (0.860-0.967)	≤130	<0.001	82.9	85.0
GPR	0.966 (0.929-1.000)	>37.72	<0.001	91.4	98.1
NLR	0.918 (0.872-0.964)	>2.84	<0.001	82.9	86.9
MPR	0.960 (0.925-0.994)	>0.033	<0.001	88.6	94.4
Lactate	0.882 (0.801-0.964)	>3.1	<0.001	80.0	93.5
Prolactin	0.976 (0.949-1.000)	>39.1	<0.001	97.1	97.2
Cortisol	0.830 (0.742-0.917)	>38.4	<0.001	71.4	84.1

GPR: Glucose/potassium ratio, NLR: Neutrophil/lymphocyte ratio, MPR: MPV/PLT ratio, AUC: Area under curve, Data were presented with St_β and 95% confidence interval; St_β: standard regression coefficient

of peripheral blood NLR, MPV, and RDW has been reported as three new indicators for inflammation.[24] Goksugur *et al*.[19] suggested that NLR and RDW values could be simple, effective, and practical measurement parameters that could help in distinguishing FS types. In addition, high NLR and MPR levels seem to be associated with an increased risk of FS.[5] In our study, significant differences between control, simple and complicated FS groups for WBC, PLT, N, L, NLR, and MPV, MPR, Hb, and Htc levels were found.

Aminoff *et al*.[20] stated an increase in plasma ACTH, beta-endorphin, beta lipotropin, prolactin, cortisol, and vasopressin levels shortly after the seizure.

Prolactin is a polypeptide hormone secreted mainly by the anterior pituitary gland, but also in other tissues and organs such as adipose tissue, uterus, and immune cells. In addition to milk production, prolactin is considered to play a role in the regulation of the immune system, behavior, and metabolism.In some studies, serum prolactin values were found to be higher in FS group compared to controls.[21] Also, it has been reported that high serum prolactin levels in adults and older children may be useful in distinguishing epileptic seizures from psychogenic or non-epileptic seizures.[6]

Thébault-Dagher *et al*.[22] showed that patients with simple FS may have higher cortisol reactivity to stress than complex FS. In their study, Dirik *et al*.[23] found significantly higher prolactin levels in the epileptic group than in children with FS and syncope attacks. On the other hand, serum cortisol levels were determined to be nonspecifically high

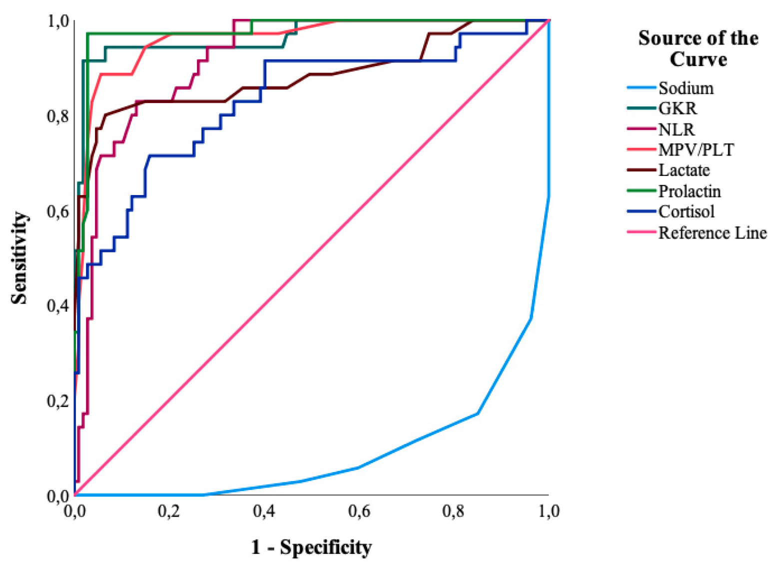

Figure 2. ROC Curve for complicated febrile seizure development

in children with epilepsy, FS, and syncope attacks.

Mehta *et al*.[24] stated that plasma cortisol levels are triggered non-selectively by all stressful events, but postictal PRL estimation can help differentiate pseudo-seizures. In this study, statistical significance was found for control, simple and complicated FS for prolactin and cortisol levels. It was found that cut-off values of prolactin >39.1 and cortisol >38.1 could guide the differentiation of complicated seizures.

Stress hyperglycemia is defined as blood glucose levels that usually exceed 150 mg/dl and then return to normal values in the context of acute illness or injury.[25] In some cases, such as carbon monoxide poisoning, a high value has been reported to be associated with a poor prognosis.[26] Güneş *et al*.[1], in their study with 169 children presenting with the first episode of FS and 189 controls, reported that the blood sugar of children with FS was significantly higher than the control groups, but the potassium was significantly lower.In line with the literature, our study demonstrated that, high glucose and low K levels may be important in these patients. In addition, it is the first study to compare patients with simple and complicated FS, and the first to report that the calculation of the GPR value may be an important parameter in this patient group.

Costea *et al*.[10] found higher lactate levels in children with complex febrile seizures and especially those with long seizure duration. We also found statistically significant high lactate levels in patients with complicated FS.

The limitations of our study are that our study is single-center and retrospective, also we have no data about whether there is a family history of epilepsy or febrile seizures in the control group patients and on which day of fever theyadmitted to the hospital.

In conclusion, our study is one of the rare studies evaluating the benefit of laboratory tests for patients presenting with FS. In our clinical practice, laboratory tests are frequently performed on pediatric patients admitting to the emergency department, and we tried to demonstrate the importance of these analyzes in FS and their value in the differentiation of FS types. These tests should be evaluated with available data for each case. We consider NLR, MPR, GPR, Na, lactate, prolactin, and cortisol measurements to be simple, effective, and practical tests in the management of FS patients and in the differential diagnosis of FS types.

DISCLOSURE

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Conflict of interest: None

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