ORIGINAL ARTICLE

Evaluation of Diagnostic Value of Blood Indices associated with Microcytic Anemia in Febrile Seizures in children

SHAQAYEQ KHOSRAVI[1], SAYED MOHAMMAD HADI SADATI[2], VAHIDEH AL_SADAT SHERAFAT[3], ZAHRA BAZARGANI[2*]
[1]*Emergency Medicine Management Research Center, Iran University of Medical Sciences, Aliasghar children Hospital, Tehran, Iran*
[2]*Department of Pediatrics, Fasa University of Medical Sciences, Fasa, Iran*
[3]*School of Medicine, Fasa University of Medical Sciences, Fasa, Iran*
**Correspondence to Zahra Bazargani M.D. Email: zahbaz@yahoo.com Tel: +989171111204*

ABSTRACT

Background: In the first years of life due to insufficient iron supply, iron deficiency anemia is one of the most common causes of anemia in children. Febrile seizures are the most common seizure disorder in childhood, and anemia, especially iron-deficiency anemia, can predispose children to seizures by affecting nervous system function.
Aim: To evaluate the blood indices associated with microcytic anemia in seizures caused by pediatric fever.
Methods: In this retrospective case-control study, the data of the complete blood count belonging to 100 children with febrile seizures and 100 children with fever of unknown focus without seizures in the age range of 6 to 60 months that were admitted to Hazrat Vali-e-Asr Hospital in Fasa, Iran, from 2016 to 2018, were extracted and compared in terms of measurable and calculated blood parameters.
Results: The incidence of febrile seizures was higher in boys than girls. This study did not show a significant difference in terms of other demographic indicators. Hb, Hct and NLR blood indices showed statistically significant differences between the control group and patients with febrile seizures. There were statistically significant differences in blood indices of Hb, MCV, MCH, NLR, S&L, and Bordbar in the control and case groups of patients with microcytosis. There was a significant difference in the amount of NLR between the three control groups and patients with seizures due to simple and complex fever, in terms of blood parameters.
Conclusion: The results of this study suggest the use of NLR as a predictor of febrile seizures. Although the mean value of most of the blood indices discussed in patients with febrile seizures was in favor of iron deficiency compared to the control group, there was no statistically significant difference between them.
Keywords: Febrile Seizures - Iron deficiency anemia - Microcytosis – Mentzer index

INTRODUCTION

Febrile seizure (FS) is one of the most common seizures in children, affecting 2 to 5 percent of all children, or 4.8 per 1,000 children each year[1]. According to the National Institutes of Health, FS occurs in infancy or childhood, usually between the ages of six months and five years, with a fever above 38°C, but it is not associated with any evidence of intracranial infection (e.g., infection, trauma to the head, and epilepsy) or any specific cause for seizure (e.g. electrolyte imbalance, hypoglycemia, drug use, or drug withdrawal)[2,3]. Pathophysiological examination of FS shows that FS could be an age-dependent response of the immature brain to fever, as studies in animal models have shown that neurostimulation increases during the brain maturation process. This hypothesis is supported by the fact that FS often occurs between 6 months and 3 years of age (65% to 85%) and mostly at 18 months of age[4,5]. In addition, it has been shown that deficiencies in important elements and specific enzymes in the oxidative system can affect the central nervous system, therefore, weakening the antioxidant defense mechanisms and increasing the level of free radicals can lead to seizures[6]. Thus, electrolyte imbalance and deficiency of micronutrients such as zinc, selenium, magnesium, copper, and iron in malnutrition and stunted growth, can predispose children to febrile seizures[7-10]. Since one of the dangers of FS is the possibility of turning it into permanent seizure and epilepsy in the future, various studies have examined risk factors to identify modifiable factors and reduce the prevalence of FS and, consequently, the prevalence of epilepsy and seizures[11,12].

Iron deficiency is the most common dietary deficiency and can lead to iron deficiency anemia by reducing hemoglobin production, which can be corrected and treated. With the development of iron deficiency, the size of red blood cells and the amount of hemoglobin decrease (microcytic and hypochromic), and the blood cells take an abnormal shape[13,14]. Iron is required for brain metabolism, neurotransmitter metabolism, and myelination of neurons, also, can alter the amplitude and threshold of neuronal stimulation[15].

Studies on the role of iron deficiency in fever-induced seizures have reported contradictory results. The possibility of decreasing the seizure threshold and increasing the risk of FS by iron deficiency anemia has been discussed in many studies[16,17]. However, some studies have reported that children with iron deficiency anemia are not prone to FS and it may even have a protective effect[18,19].

Therefore, considering the obvious contradiction in the results of previous studies and also the importance of diagnosing febrile seizures and differentiating its types in order to properly control the disease process, timely treatment, and evaluation of risk factors that may expose the patient to recurrent febrile seizures, this study was conducted to investigate the role of iron as one of the most influential factors in pediatric FS.

MATERIALS AND METHODS

Patients: In this retrospective case-control study, patients in the age range of 6 to 60 months that were admitted to Hazrat Vali-e-Asr Hospital in Fasa, Iran, from 2016 to 2018, were examined. The sample size required for the present study, according to the study by Eda Ozaydin et al. and using Stata 11 software, was considered to be a total of 200 patients so that 100 patients with a primary diagnosis of febrile seizure in one group and another 100 patients with a primary diagnosis of fever of unknown focus and without seizure in the other group, were evaluated. Patients with a history of non-febrile seizures, developmental-neurological problems, metabolic disorders, use of anticonvulsants, and blood transfusions in the case group, and cases with a history of any type of seizures in the control group, were excluded from the study. Also, all the information and secrets in the patients' files were kept confidential and the study with the ethics code of IR.GUMS.REC.1398.o89 was approved by the National Ethics Committee in Biomedical Research.

Evaluation of patients: Based on the information obtained from the patients' files, patients were divided into three groups: children with seizures due to simple fever, children with seizures due to complex fever, and children with fever of unknown focus and without seizures. Patients were evaluated for age, gender, age at birth, birth weight, family history of FS, and epilepsy, as well as possible complications.

The data of the complete blood count of the patients were extracted from the patients' files and evaluated. For the CBC test, patient blood samples were collected in a tube containing Ethylenediaminetetraacetic acid (EDTA) and analyzed by Cismax K21. Blood indices differentiating microcytic anemia were calculated for all patients using the formulas in the study by Pessar S et al.

Statistical analysis: Data were analyzed in Stata 11 software. Independent t-test, Kruskal-Wallis, and Mann-Whitney U non-parametric tests were used to compare quantitative variables in the two groups. In order to compare the qualitative variables in the two groups, a chi-square test was used and logistic regression was used to estimate OR. The significance level in this study was considered less than 0.05.

RESULTS

In the present study, patients in the FS group were divided into two levels: simple (n = 93) and complex (n = 7). The mean age of patients showed that there was no significant difference between the two groups (P = 0.487) (Table 1). Also, in terms of gender, according to Table 1, in the group of children with FS (simple and complex) were a total of 69 boys and 31 girls, and in the control group were 56 and 44 boys and girls, respectively, which demonstrated a statistically significant difference. (P = 0.035).

Also, the study of underlying variables in patients with simple FS compared to patients with FS complex showed that in terms of variables of gestational age, family history of epilepsy, family history of febrile seizures, history of previous febrile seizures, birth weight, and weight at hospitalization, there was no statistically significant difference between the two groups (P> 0.05) (Table 2).

Examination of blood indices in control groups and FS patients showed that indices of Hb (P = 0.029), Hct (P = 0.045), l.count (P = 0.002), n.count (P = 0.001), and NLR (P = 0.000), were significantly different in the control group and patients with FS (Table 3).

Also, according to Table 4, which shows the comparison between the control group and patients with simple and complex FS in terms of blood indices, L.Count, N.Count, and NLR were significantly different (P <0.05). However, in the comparison between patients with seizures caused by simple and complex fever, no significant difference was observed in terms of blood indices (P> 0.05).

Table 1. Comparison of patients in terms of age and gender

Variables		Control group (n = 100)	SFS group (n = 93)	CFS group (n = 7)	P value
Age(month)		21.9±12.6	23.3±10.3	26.5±14.5	0.487
Gender	male	56(56%)	62(66.7%)	10(100%)	0.035
	female	44(44%)	31(33.3)	0(0%)	

Table 2. Comparison of patients in terms of underlying variables

Variables	SFS group (n = 93)	CFS group (n = 7)	P value
Gestational age			
37week<	6.7%	0%	0.594
37week>	93.3%	100%	
Family history of epilepsy			
Absent	92.5%	100%	0.452
Present	7.5%	0%	
Family history of FC			
Absent	89.2%	85.7%	0.773
Present	10.8%	14.3%	
Past history of FC			
Absent	82.8%	100%	0.231
Present	17.2%	0%	
Birth weight (g)	3025±548.5	3125±377.4	0.724
Weight (g)	11342±2110	11920±1792.2	0.551

Table 3: Comparison of blood indices in the control group and patients with febrile seizures

	Total Pt	Control n=100		F.S n=100		P.Value
		Mean	S.D	Mean	S.D	
IDA	WBC X1000/mm3	10.347	4.899	10.732	4.818	0.533
	RBC X1000000/ml	4.535	0.486	4.585	0.468	0.477
	HB g/dl	11.223	1.043	11.533	1.072	*0.029*
	HCT %	33.973	2.823	34.646	2.798	*0.045*
	MCV fl	75.414	6.533	75.698	5.066	0.453
	MCH pg	24.967	2.873	25.283	2.137	0.701
	MCHC g/dl	33.042	1.589	33.347	1.489	0.088
	PLT x1000/µl	296.570	107.305	286.560	88.416	0.760
	l.count x 1000/mm3	4.139	2.480	3.206	2.353	*0.002*
	n.count x 1000/mm3	5.263	3.649	6.554	3.204	*0.001*
	NLR	1.990	2.669	3.066	3.080	*0.000*
> 13	Mentzer.I	16.920	2.936	16.739	2.445	0.503
>1530	S & L	1455.456	373.376	1469.042	297.112	0.686
>3.8	Srivastava	5.614	1.125	5.594	0.875	0.862
>27	Sirdah	37.210	6.264	36.514	5.869	0.321
>15	Ehsani	30.067	10.460	29.849	8.711	0.470
>0	E & F	11.364	6.692	10.048	7.055	0.219
<1.7	MDHL	1.495	0.141	1.529	0.159	0.153
<0.304	MCHD	0.330	0.016	0.334	0.014	0.073
321-370	Kerman1	429.590	115.000	427.013	89.466	0.745
105-130	Kerman2	129.252	31.546	127.838	25.758	0.509
<44	Bordbar	26.650	51.279	16.777	33.090	0.765

Table 4. Comparison of blood indices between the control group and patients with seizures caused by simple and complex fever

ROUP	control n=100		complex n=7		simple n=93		P.Value
	Mean	S.D	Mean	S.D	Mean	S.D	
WBC X1000/mm3	10.347	4.899	9.543	4.101	10.822	4.875	0.599
RBC X1000000/ml	4.535	0.486	4.560	0.298	4.587	0.480	0.767
HB g/dl	11.223	1.043	11.143	0.673	11.562	1.093	0.052
HCT %	33.973	2.823	33.429	1.838	34.738	2.843	0.053
MCV fl	75.414	6.533	73.429	3.196	75.869	5.150	0.255
MCH pg	24.967	2.873	24.486	1.552	25.343	2.169	0.364
MCHC g/dl	33.042	1.589	33.329	0.867	33.348	1.528	0.230
PLT x1000/µl	296.570	107.305	280.143	53.794	287.043	90.665	0.948
l.count x 1000/mm3	4.139	2.480	2.570	1.524	3.254	2.403	*0.007*
n.count x 1000/mm3	5.263	3.649	6.108	3.291	6.588	3.213	*0.005*
NLR	1.990	2.669	3.600	3.077	3.026	3.093	*0.000*
Mentzer.I	16.920	2.936	16.185	1.567	16.781	2.499	0.583
S & L	1455.456	373.376	1328.252	193.722	1479.639	301.535	0.296
Srivastava	5.614	1.125	5.401	0.620	5.608	0.892	0.706
Sirdah	37.210	6.264	35.440	3.255	36.595	6.023	0.448
Ehsani	30.067	10.460	27.829	5.443	30.001	8.910	0.456
E & F	11.364	6.692	9.754	3.823	10.070	7.252	0.437
MDHL	1.495	0.141	1.519	0.089	1.530	0.163	0.358
MCHD	0.330	0.016	0.333	0.009	0.334	0.015	0.194
Kerman1	429.590	115.000	397.972	59.771	429.199	91.166	0.550
Kerman2	129.252	31.546	119.174	15.764	128.490	26.298	0.429
Bordbar	26.650	51.279	20.566	19.957	16.492	33.928	0.320

In this study, 26 patients in the control group and 24 patients with febrile seizures who were microcytic according to age and amount of MCV (age 6 to 23 months with MCV less than 70 and age 24 to 60 months with MCV less than 75) were compared in terms of blood parameters. Among them, the differences in blood indices of Hb, MCV, MCH, L.Count, N.Count, NLR, S&L, and Bordbar were statistically significant (P <0.05) (Table 5).

Due to the significant differences between NLR and Hb indices in the study of all FS and microcytic patients based on statistical tests, ROC diagrams for comparison are given in Figure 1. The NLR index in predicting the onset of febrile seizures in microcytic patients had a sensitivity of 79.2% and a specificity of 76.9%. This index had a sensitivity of 75% and a specificity of 57% to predict the incidence of febrile seizures in the total group. Also, the

Hb index had 66.7% sensitivity and 65.4% specificity in microcytic patients and showed the difference between case and control groups with 49% sensitivity and 67% specificity.

Table 5. Comparison of blood indices in microcytic patients of the control group and patients with febrile seizures

	Microcytic Pt	Control n=26		F.S n=24		P.Value
		Mean	S.D	Mean	S.D	
IDA	WBC X1000/mm3	10.650	5.464	11.179	6.314	0.985
	RBC X1000000/ml	4.973	0.487	4.929	0.554	0.877
	HB g/dl	10.754	1.215	11.521	1.247	*0.026*
	HCT %	33.204	2.908	34.638	3.463	0.077
	MCV fl	67.100	5.749	70.571	4.927	*0.016*
	MCH pg	21.785	2.921	23.558	2.461	*0.029*
	MCHC g/dl	32.358	1.828	33.221	1.734	0.072
	PLT x1000/µl	346.462	135.292	306.042	113.994	0.252
	l.count x 1000/mm3	5.370	3.181	3.360	2.783	*0.005*
	n.count x 1000/mm3	4.417	3.171	6.812	3.707	*0.014*
	NLR	1.052	1.016	2.696	1.928	*0.000*
> 13	Mentzer.I	13.682	2.204	14.553	2.362	0.313
>1530	S & L	1008.141	286.972	1193.590	255.753	*0.040*
>3.8	Srivastava	4.454	0.913	4.871	0.944	0.177
>27	Sirdah	29.866	4.734	31.079	5.086	0.509
>15	Ehsani	17.373	9.425	21.279	9.058	0.203
>0	E & F	4.958	5.271	4.638	6.361	0.698
<1.7	MDHL	1.604	0.136	1.637	0.155	0.372
<0.304	MCHD	0.323	0.019	0.333	0.015	0.057
321-370	Kerman1	303.304	83.335	347.269	84.624	0.111
105-130	Kerman2	92.823	21.485	103.745	21.821	0.111
<44	Bordbar	82.783	75.116	43.523	57.205	*0.034*

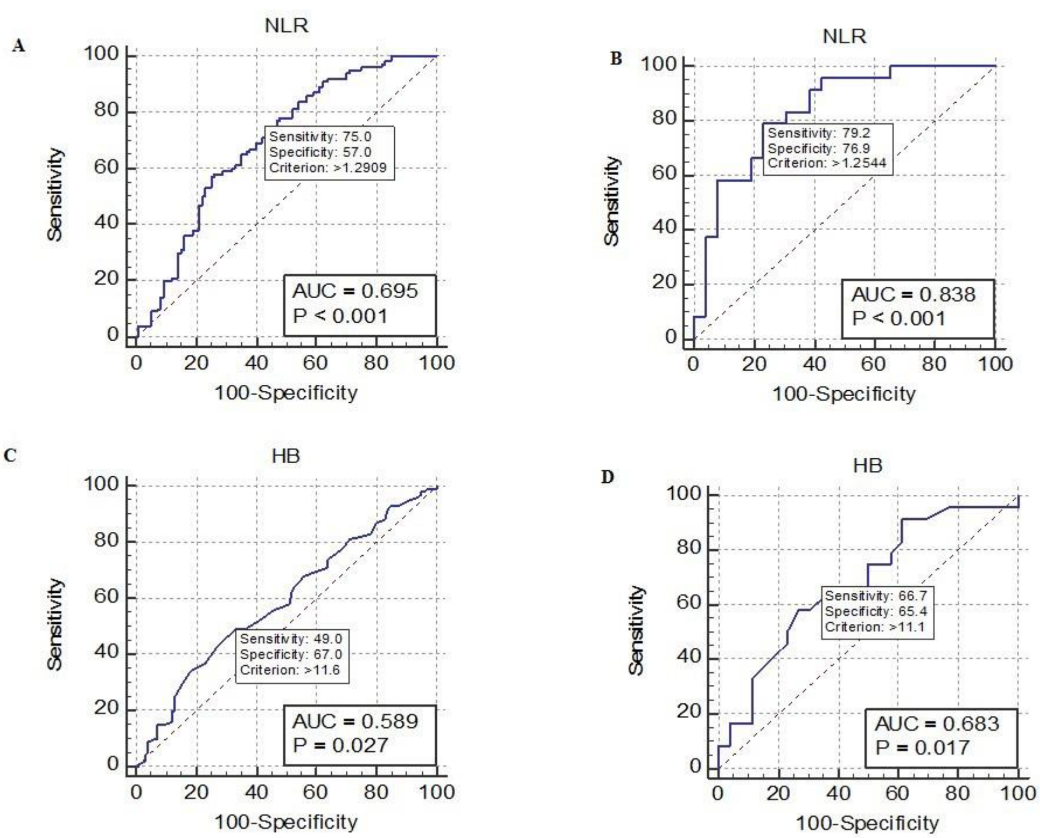

Figure 1. Comparison of sensitivity and specificity of NLR (A&B) and Hb (C&D) indices in microcytic and total groups

DISCUSSION

Due to the effects of anemia and especially the most common type of it which is iron deficiency anemia, the possibility of its effect on the occurrence of seizures in FS patients is given. Children's eating habits and diet play an important role in absorbing and storing iron and preventing iron deficiency anemia[20].

The aim of this study was to evaluate the blood indices associated with microcytic anemia in pediatric FS. Based on the results of our study, the male gender was suggested as a risk factor for febrile seizures. Similar to our results, Sharawat et al. stated that the majority of children with FS were boys under 2 years of age[4]. Fetveit et al. also showed that the peak incidence of FS in children was at 18 months of age[21]. In addition, in the present study, no significant relationship was observed between underlying variables such as gestational age, family history of epilepsy, family history of febrile seizures, previous febrile seizures, birth weight, and weight at the time of referral to the hospital, in the evaluation of patients with seizures due to simple and complex fever. In this study, the number of people with complex febrile seizures was 7 and the number of people with simple febrile seizures was 93. This lack of association between underlying variables and FS may be justified by the low number of patients with complex febrile seizures. However, Mahyar A et al. Showed that 55% of patients with FS had a positive family history[22] and another study by Hesdorffer DC et al reported the effect of family history was 10-45%[23].

In this study, there were statistically significant differences between L.Count, N.Count, and NLR blood indices in the comparison between the control group and patients with febrile seizures. Zhigang Liu et al. also stated that an increase in NLR and the ratio of mean platelet volume to platelet count (MPR) was associated with an increased risk of FS[24]. In another study, S.B. Goksugur et al. stated that the levels of NLR and RDW in the FS complex have increased and they appear to be critical indicators in the assessment and differentiation of febrile seizures. They also stated that the underlying mechanism of the association between NLR and complex febrile seizures is unclear but may be dependent on interleukin-1 beta, which is the precursor to fever, and the neutrophil counts and their migration to body tissues[25]. Studies show that fever is triggered by proinflammatory cytokines such as interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha (TNF-α) during infection[26]. According to data from a large number of studies, inflammation, which itself causes a fever response, is involved in the development of febrile seizures. It has been suggested that inflammatory cytokines, especially interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha, may play an important role in the development of febrile seizures[27,28]. Although inflammatory cytokines are useful biomarkers, increased price and limited access to measure them are the barriers to use. NLR, MPV, and RDW are three new indicators for the study of inflammation that, due to their widespread use and low cost compared to other inflammatory markers, have received much attention as predictors associated with predisposing factors for febrile seizures and its differentiation[29].

Also, according to the results of our study, Hb and Hct blood indices were significantly different in the comparison between the control group and patients with febrile seizures. In addition, MCV, Hb, MCH, S&L and Bordbar blood indices were statistically different in microcytic patients of control and FS groups. Comparison of sensitivity and specificity of Hb and NLR indices according to ROC diagrams in the total group and the group of microcytic patients also showed that the statistical difference between the data was more pronounced in the microcytic group, so in the microcytosis group, these indices had more predictive value. In a study of hemogram indices in different types of febrile seizures, ÖRNEK et al. Showed that Hb, HCT, MPV, NLR, and platelet lymphocyte ratio (PLR) were significantly different between simple and complex FS groups[30]. Platelets have been shown to play an important role not only in homeostasis, but also in the immune system and inflammation, and the resulting inflammation can increase the excitability of neurons in the brain and decrease the seizure threshold[31,31]. In this regard, studies have been conducted to investigate the relationship between platelet indices and FS[24,33]. Platelet counts, including PLT, MPV, PDW, and PCT, all indicate platelet activity. MPV reflects platelet size and platelet production in the bone marrow. This index can be considered as a marker of platelet activation that does not involve any additional costs and is a suitable method for examining several diseases as an indicator of platelet activation and the severity of inflammation[34,35].

On the other hand, studies have shown that there is a direct relationship between iron deficiency and a reduced risk of fever. It has been suggested that iron-induced brain fat peroxidation may lead to febrile seizures. In addition, cell membrane uptake and secretion of dopamine, gamma-aminobutyric acid, and other neurotransmitters may be affected by iron. Thus, the seizure threshold may increase due to iron deficiency[36].

In general, although the mean value of most of the blood indices discussed in patients with febrile seizures was in favor of iron deficiency compared to the control group, there was no statistically significant difference between them. This finding may be due to the significant prevalence of thalassemia minor alone or thalassemia minor associated with iron deficiency anemia in the region. Therefore, according to the mentioned points, it seems that the inclusion of more patients in the study in proportion to the prevalence of iron deficiency anemia and thalassemia minor could be helpful in proving the hypotheses considered in the study. On the other hand, due to the fact that this study was retrospective and did not mention the amount of RDW in the patients' test, it was not possible to use some of the considered blood indices, which are suggested to be considered in future studies.

CONCLUSION

The results of this study showed that NLR could be used as a predictive indicator of FS. Although the mean value of most of the blood indices discussed in patients with febrile seizures was in favor of iron deficiency compared to the control group, there was no statistically significant difference between them. This finding may be due to the significant prevalence of thalassemia minor alone or thalassemia minor associated with iron deficiency anemia in the region, which requires a study with a wider statistical population.

Acknowledgement: The authors thank the Fasa University of Medical Sciences for supporting this research.

REFERENCES

1. Chung S. Febrile seizures. *Korean journal of pediatrics*. 2014;57(9):384-95.
2. Leung AK, Hon KL, Leung TN. Febrile seizures: an overview. *Drugs in context*. 2018;7:212536.
3. Leung AK. Common Problems in Ambulatory Pediatrics: Specific Clinical Problems, Volume 1: Nova Science Publishers, Incorporated; 2012.
4. Sharawat IK, Singh J, Dawman L, Singh A. Evaluation of Risk Factors Associated with First Episode Febrile Seizure. *Journal of clinical and diagnostic research : JCDR*. 2016;10(5):Sc10-3.
5. Laino D, Mencaroni E, Esposito S. Management of Pediatric Febrile Seizures. *International Journal of Environmental Research and Public Health*. 2018;15(10).
6. Balci O, YILMAZ D. Serum selenium and copper levels in children with simple febrile seizure and viral infections. *Pediatric practice and research*. 2014;2(1).
7. Sadeghzadeh M, Khoshnevisasl P, Koosha A, NorouziPakdel M. The relation between serum zinc level and febrile seizures in children admitted to Zanjan Valie-Asr hospital. *J Adv Med Biomed Res*. 2011;19(74):17-24.
8. Mahyar A, Ayazi P, Fallahi M, Javadi A. Correlation between serum selenium level and febrile seizures. *Pediatric neurology*. 2010;43(5):331-4.
9. Srinivasa S, Manjunath M. Serum zinc levels in children with febrile seizures. *Journal of evolution of medical and dental sciences*. 2014;3(12):2983-9.
10. Afshar Khas L, Tavasoli A, Shamel S. Comparison of magnesium serum levels in children with febrile convulsion and febrile children without seizure. *Razi journal of medical sciences*. 2014;21(121):73-7.
11. Dreier JW, Li J, Sun Y, Christensen J. Evaluation of Long-term Risk of Epilepsy, Psychiatric Disorders, and Mortality Among Children With Recurrent Febrile Seizures: A National Cohort Study in Denmark. *JAMA Pediatr*. 2019;173(12):1164-70.
12. Surani MK, Yousuf M, Saleem K, Khan S, Ahmad M, Altaf MS. Iron deficiency anemia among children with febrile seizures. *The Professional Medical Journal*. 2020;27(09):1922-6.
13. Kim EA, Lim YT, Hah JO, Sohn YB, Kim YK, Choi JH, Kim SY, Jang KM, Ahn J, Lee JM. Neuronopathic Gaucher disease presenting with microcytic hypochromic anemia. *International journal of hematology*. 2019;109(3):361-5.
14. Elstrott B, Khan L, Olson S, Raghunathan V, DeLoughery T, Shatzel JJ. The role of iron repletion in adult iron deficiency anemia and other diseases. *European journal of haematology*. 2020;104(3):153-61.
15. Ferreira A, Neves P, Gozzelino R. Multilevel Impacts of Iron in the Brain: The Cross Talk between Neurophysiological Mechanisms, Cognition, and Social Behavior. *Pharmaceuticals (Basel, Switzerland)*. 2019;12(3).
16. Madan N, Rusia U, Sikka M, Sharma S, Shankar N. Developmental and neurophysiologic deficits in iron deficiency in children. *Indian journal of pediatrics*. 2011;78(1):58-64.
17. Aziz KT, Ahmed N, Nagi AG. Iron Deficiency Anaemia As Risk Factor For Simple Febrile Seizures: A Case Control Study. *J Ayub Med Coll Abbottabad*. 2017;29(2):316-9.
18. Johnston MV. Iron deficiency, febrile seizures and brain development. *Indian pediatrics*. 2012;49(1):13-4.
19. Bidabadi E, Mashouf M. Association between iron deficiency anemia and first febrile convulsion: A case-control study. *Seizure*. 2009;18(5):347-51.
20. Kim J, Wessling-Resnick M. Iron and mechanisms of emotional behavior. *The Journal of nutritional biochemistry*. 2014;25(11):1101-7.
21. Fetveit A. Assessment of febrile seizures in children. *Eur J Pediatr*. 2008;167(1):17-27.
22. Mahyar A, Ayazi P, Fallahi M, Javadi A. Risk factors of the first febrile seizures in Iranian children. *Int J Pediatr*. 2010;2010:862897.
23. Hesdorffer DC, Shinnar S, Lewis DV, Nordli DR, Jr., Pellock JM, Moshé SL, Shinnar RC, Litherland C, Bagiella E, Frank LM, et al. Risk factors for febrile status epilepticus: a case-control study. *J Pediatr*. 2013;163(4):1147-51.e1.
24. Liu Z, Li X, Zhang M, Huang X, Bai J, Pan Z, Lin X, Yu D, Zeng H, Wan R, 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(1):15123.
25. Goksugur SB, Kabakus N, Bekdas M, Demircioglu F. Neutrophil-to-lymphocyte ratio and red blood cell distribution width is a practical predictor for differentiation of febrile seizure types. *Eur Rev Med Pharmacol Sci*. 2014;18(22):3380-5.
26. Kany S, Vollrath JT, Relja B. Cytokines in Inflammatory Disease. *Int J Mol Sci*. 2019;20(23).
27. Kim K, Kwak BO, Kwon A, Ha J, Kim SJ, Bae SW, Son JS, Kim SN, Lee R. Analysis of plasma multiplex cytokines and increased level of IL-10 and IL-1Ra cytokines in febrile seizures. *Journal of neuroinflammation*. 2017;14(1):200.
28. Kwon A, Kwak BO, Kim K, Ha J, Kim SJ, Bae SH, Son JS, Kim SN, Lee R. Cytokine levels in febrile seizure patients: A systematic review and meta-analysis. *Seizure*. 2018;59:5-10.
29. Büyükaslan H, Asoğlu M. Evaluation Of Mean Platelet Volume, Red Cell Distributed Width And Neutrophil To Lymphocyte Ratio In Conversion Disorder. *Neuropsychiatric disease and treatment*. 2019;15:2879-84.
30. Örnek Z, Kardeş H, Pİşkİn İE, Çalik M. Comparison of Hemogram Parameters in Febrile Seizures Types. *Düzce Tıp Fakültesi Dergisi*. 2020;22(1):1-6.
31. Ali RA, Wuescher LM, Worth RG. Platelets: essential components of the immune system. *Current trends in immunology*. 2015;16:65-78.
32. Vezzani A, Friedman A, Dingledine RJ. The role of inflammation in epileptogenesis. *Neuropharmacology*. 2013;69:16-24.
33. Abuhandan M, Solmaz A, Geter S, Kaya C, Guzel B, Yetkin I, Koca B. Evaluation of selenium levels and mean platelet volume in patients with simple febrile convulsion. *Iranian journal of pediatrics*. 2014;24(4):401-5.
34. Yildiz Y, Cakmak S, Calapoglu T, Hocoglu Z, Karadeniz E, Ozkasap S. Mean platelet volume can be used as a hospitalization criteria in pediatric patients diagnosed with acute bronchiolitis. 2018.
35. Yigit Y, Yilmaz S, Akdogan A, Halhalli HC, Ozbek AE, Gencer EG. The role of neutrophil-lymphocyte ratio and red blood cell distribution width in the classification of febrile seizures. *Eur Rev Med Pharmacol Sci*. 2017;21(3):554-9.
36. Soheilipoor F, Tavasoli A, Babasafari Renani Z. The Association between Failure to Thrive or Anemia and Febrile Seizures in Children between 6 Months to 6 Years Old Age. *Iranian journal of child neurology*. 2018;12(3):86-93.