

Hyperglycemia and hyponatremia in predicting the recurrence of febrile convulsions

 Ilknur Surucu Kara

Department of Pediatric, Faculty of Medicine, Binali Yildirim University, Erzincan, Turkey

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Abstract

Aim: The most common seizure type in childhood is febrile convulsion, which is likely to recur due to many risk factors. This study aimed to evaluate serum sodium and glucose levels in patients who had a febrile convulsion and investigate the relationship between these values and recurrent seizures.

Materials and Methods: The medical records of patients presenting to our hospital with the diagnosis of febrile convulsion between 2013 and 2018 were investigated.

Patients with high-risk factors for recurrence were excluded. According to the reference ranges of our laboratory, for glucose, 101-149 mg/dl as mild-to-moderate stress hyperglycemia, above 150 mg/dl as severe stress hyperglycemia; for sodium, below 134 mmol/L as hyponatremic.

Results: Of the 90 patients, 51 were boys, and 39 were girls. Without recurrent convulsions with recurrent convulsions (first-last): The mean age was 27.2 ± 12.7 months / 27.4 ± 11.3 months- 30.5 ± 12.4 ; the mean serum glucose level was 129.1 ± 37 mg/dl/ 130 ± 37.5 mg/dl- 124 ± 34 mg/dl; the mean serum sodium level was 134.07 ± 3.05 mmol/L 134.4 ± 2.6 mmol/L- 133.8 ± 2.9 mmol/L. The glucose level was 60-100 mg/dl in 14/5 cases, 101-149 mg/dl in 39/10 cases, and above 150 mg/dl in 16/6 cases; the sodium level was 135-150 mmol/L in 29/10 cases, < 135 mmol/L in 40/11 cases.

Conclusion: Febrile convulsion is in most cases present with hyponatremia and hyperglycemia, but this cannot be a predictive marker of seizure recurrence.

Keywords: Febrile seizures; hyponatremia; hyperglycemia; pediatrics

INTRODUCTION

Febrile seizures are usually benign seizures most commonly seen in children aged six to 60 months. The prevalence of febrile seizures is approximately 2-5%, varying from one country to another. There is a possibility of recurrence in one-third of the cases (1). For the definition of febrile seizures, there should not be a history of epilepsy diagnosis, central nervous system infections should be excluded, and the seizure should occur at a body temperature of higher than 38 °C. These seizures are classified as complex if they last longer than 15 minutes, occur focally and recur within 24 hours, and considered as simple if there is full-body involvement lasting less than 15 minutes and presenting without recurrence within 24 hours (2).

Genetic predisposition, seizures under one year of age, and seizures accompanied by low fever are risk factors for recurrence (1). After the first seizure, repetition can be seen in 15-70% of the cases within the first two years and

16% within 24 hours (3, 4). Despite studies suggesting that serum sodium levels in recurrent febrile seizures are significantly lower compared to non-recurrent seizures, there are also researchers reporting no significant difference (4). It has also been shown that stress hyperglycemia may be present in febrile convulsion, and it is associated with the severity of seizures but not with recurrence (5).

This study aimed to evaluate sodium and glucose levels in patients presenting to our hospital with febrile convulsions, to investigate the relationship between these values and recurrent seizures, and to determine whether sodium and glucose levels in febrile convulsions can help identify possible recurrences.

MATERIALS and METHODS

After receiving the approval of the ethics committee, the medical records of patients presenting to Erzincan Binali Yildirim University Department of Pediatrics with febrile convulsions between 2013 and 2018 were obtained from

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Corresponding Author: Ilknur Surucu Kara, Department of Pediatric, Faculty of Medicine, Binali Yildirim University, Erzincan, Turkey

E-mail: drilknursurucu@gmail.com

the automated system of the hospital. Patients fewer than six months or above 60 months, those diagnosed with epilepsy or convulsion, metabolic disease or neurological disease, mental retardation and abnormal serum values that might cause attacks and those who presented to the hospital with a seizure but were then diagnosed with a central nervous system infection were excluded from the study. Patients who several risk factors for recurrence such as complex febrile seizures, patients under one year old, children with a family history of febrile convulsions, brief duration between the onset of fever and the initial convulsion, lower body temperature during convulsion were excluded from the study. In recurrences, age, gender, and serum sodium and glucose levels at initial and recurrent seizures were recorded for pediatric cases with available anamnesis information and examination findings. The reference ranges of our laboratory are 60-100 mg/dl for average glucose and 135-150 mg/dl for normal sodium. Accordingly, 101-149 mg/dl glucose was considered as mild-to-moderate stress hyperglycemia and above 150 mg/dl as severe stress hyperglycemia, below 135 mmol/L was considered as hyponatremia. Patients with a serum sodium value of <120 mmol/L and >150 mmol/L were excluded from the study due to the possibility that this caused the convulsions. Glucose levels were grouped as normal glucose levels, mild-to-moderate stress hyperglycemia, and severe stress hyperglycemia in all patients. Then the rates of recurrence between the three groups were analyzed. Sodium levels were grouped as normal sodium levels and hyponatremia in all patients. Then the rates of recurrence between the two groups were analyzed.

Statistical Analysis

The Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. For the evaluation of the data, descriptive

statistics (frequency, mean, standard deviation, cross tabs) were used, and the quantitative data were compared using the Wilcoxon signed-ranks test and one-sample t-test, One-Way ANOVA. The significance of the values was evaluated at $p < 0.05$ and 95% confidence interval (CI).

RESULTS

The data belonging to 90 patients with simple febrile convulsions were evaluated. Twenty-one of these patients (23.3%) were administered to the emergency department due to the recurrence of febrile seizures. Of the 90 patients, 51 were boys (56.7%), and 39 were girls (43.3%), with a male/female ratio of 1.3. The mean age was 27.3 ± 12.4 months (range: 12.2-56 months), and the mean serum glucose level was 129.3 ± 36.9 mg/dl (range: 76-249 mg/dl), the mean serum sodium level was 134.1 ± 2.9 mmol/L (range: 127-140 mg/dl).

The glucose level was found to be within the normal range in 19 patients (21.1%), 101-149 mg/dl in 49 patients (54.4%), and above the 150 mg/dl threshold in 22 cases (24.4%). The sodium level was below 135 mmol/L in 39 cases (43.3%), and 135 mmol/L or above in 51 patients (56.7%).

In patients without recurrence: 35 were boys (50.7%) and 34 were girls (49.3%), with a male/female ratio of 1.02 ($p > 0.05$). The mean age was 27.2 ± 12.7 months (range: 12.2-56 months). The mean age of the girl patients was 24.4 ± 12.2 months; the mean age of the boy patients was 29.9 ± 12.8 months ($p = 0.075$) (Table 1).

The mean glucose level was 129.1 ± 37 mg/dl (range: 76-249 mg/dl). The mean serum glucose level in girls was 126.3 ± 29.7 mg/dl, in boys was 131.8 ± 43.2 mg/dl, and these results were statistically not significant ($p = 0.542$) (Table 1).

Table 1. Evaluation of the patients with febrile convulsions

	Without recurrence n=69 (%)	With recurrence n=21 (%)		P
Girl	34 (49.3%)	5(23.8%)		
Boy	35 (50.7%)	16(76.2%)		<0.05*
	Mean ± sd	First Mean ± sd	Recurrent Mean ± sd	
Age	27.2±12.7	27.4 ± 11.3	30.5±12.4	>0.05
All patients-Glucose-mg/dl	129.1±37	130 ±37.5	124 ± 34	
glucose- girls-mg/dl	126.3±29.7	133.6±36	122.8 ± 33	>0.05
glucose-boys-mg/dl	131.8±43.2	128.8±39.1	124.3±35.4	
All patients-Sodium- mmol/L	134.07±3.05	134.4 ± 2.6	133.8 ± 2.9	
sodium-girls - mmol/L	134.3±2.4	134.8±2.1	135 ± 2.4	>0.05
sodium-boy- mmol/L	133.5±3.5	134.4±2.8	133.5 ± 3	

*= Only in recurrent seizures; n= Number of patients; sd= Standard deviation; %= Percentage of patients

The glucose level was found to be within the normal range in 14 patients (20.3%), 101-149 mg/dl in 39 patients (56.5%), and above the 150 mg/dl threshold in 16 cases (23.2%). The mean age was 30 months for normal glucose group patients, 27.2 months for those with a high glucose group, and 24.9 months for those with the higher glucose group ($p=0.560$) (Table 2).

The mean sodium level was 134.07 ± 3.05 mmol/L, ranging from 127 to 140 mmol/L. The mean serum sodium level in girls 134.3 ± 2.4 mmol/L, serum sodium level in boys 133.5 ± 3.5 mmol/L, no statistically significant difference ($p=0.454$) The mean age was 27.3 ± 12.4 months (Table 1).

The sodium level was below 135 mmol/L in 29 cases (42%), and 135 mmol/L or above in 40 patients (58%). The mean age was 26.8 months for hyponatremic patients and 27.8 months for those with a normal sodium value ($p=0.075$) (Table 2).

In patients with recurrence: 16 were boys (76.2%) and 5 were girls (23.8%), with a male/female ratio of 3.2 ($p=0.030$). The mean age of the patients was 27.4 ± 11.3 months (range: 14-54 months). The mean age of the girl patients was 24.2 ± 11.2 months, the mean age of the boy patients was 28.5 ± 11.5 months ($p=0.474$) (Table 1).

The mean glucose level was 130 ± 37.5 mg/dl (range: 87-235 mg/dl) for the first seizure and 124 ± 34 mg/dl (range: 71-229 mg/dl) for the last recurrent seizure ($p = 0.591$). The mean serum glucose level in girls was 133.6 ± 36 mg/dl

for the first seizure and 122.8 ± 33 mg/dl for the recurrent seizure ($p = 0.635$). The mean serum glucose level in boys was 128.8 ± 39.1 mg/dl for the first seizure and 124.3 ± 35.4 mg/dl for the recurrent seizure ($p = 0.736$) (Table 1).

The glucose level was found to be within the normal range in 5 patients (23.8%), 101-149 mg/dl in 12 patients (57.1%), and above the 150 mg/dl threshold in 4 cases (19%) (Table 2). The rates of the recurrence were similar in each group (Table 2).

The mean age in first seizures was 28.2 ± 12.6 months for normal glucose groups patients, 27.2 ± 12.53 months for those with a high glucose groups and 27.4 ± 11.3 months for those with a severe high glucose group ($p=0.988$). The mean age in recurrent seizures was 27.3 ± 17.2 months for normal glucose groups patients, 31.7 ± 13.3 months for those with a high glucose group and 29.2 ± 8.8 months for those with a severe high glucose group ($p=0.840$). The mean age was similar in each group.

The mean sodium level was 134.4 ± 2.6 mmol/L (range: 130-139 mmol/L) for the first seizure and 133.8 ± 2.9 mmol/L (range: 129-140 mmol/L) for the recurrent seizure ($p=0.479$). The mean serum sodium level in girls was 134.8 ± 2.1 mmol/L for the first seizure and 135 ± 2.4 mmol/L for the recurrent seizure ($p= 0.895$). The mean serum sodium level in boys was 134.4 ± 2.8 mmol/L for the first seizure and 133.5 ± 3 mmol/L for the recurrent seizure ($p= 0.410$) (Table 1).

Table 2. Glucose and sodium levels in patients

		Without recurrence n=69 (%)	With recurrence first seizure n =21 (%)	With recurrence recurrent seizure n=21 (%)	p
Sodium level	135-150 mmol/L	29 (42 %)	10 (47.6%)	8 (38.1%)	>0.05
	< 135 mmol/L	40 (58 %)	11 (52.4%)	13 (61.9%)	
Glucose level	60-100 mg/dl	14 (20.3%)	5 (23.8%)	3 (14.2%)	>0.05
	101-149 mg/dl	39 (56.5%)	10 (47.6%)	13 (61.9%)	
	≥ 150 mg/dl	16 (23.2%)	6 (28.6%)	5 (23.9%)	

n=Number of patients; %= Percentage of patients

In the first seizures in recurrent seizures: The sodium level was below 135 mmol/L in 11 cases (52%), and 135 mmol/L or above in 10 patients (52%). The mean age was 28.8 ± 12.5 months for hyponatremic patients and 26.2 ± 10.5 months for those with a normal sodium value ($p=0.623$).

In the last seizures in recurrent seizures: The sodium level was below 135 mmol/L in 8 cases (52%) and 135 mmol/L or above in 13 patients (52%). The rates of the recurrence were similar in each group (Table 2). The mean age was 37 ± 15.2 months for hyponatremic patients and 26.5 ± 8.7 months for those with a normal sodium value ($p=0.060$). The mean age was similar in each group.

DISCUSSION

In febrile convulsions that are the most common seizures of childhood, genetic predisposition, seizure history in the family, environmental factors, young age, short duration of fever before the seizure, and male gender are among risk factors for recurrence (6).

It was previously suggested that patients susceptible to infections and frequent illnesses for the male gender constitute a risk factor for the recurrence of febrile convulsions (7). Studies demonstrating a higher prevalence of febrile convulsions in boys compared to girls report the male/female ratio as 1.4/1, 1.3/1, and 1.36/1 (7,8). In the current study, the frequency of febrile

convulsions in both gender were similar in those without recurrent seizures. Aksay et al. reported that two-third of the recurrences were seen in boys, while our rate was identical (male/female: 3.2) (7).

Febrile convulsions are usually seen between 12-30 months, and most commonly at 18 months of age (7). Consistent with the literature, 62 (68.8%) of 90 patients in the current study were aged 12 to 30 months, and the prevalence was similar for the patients in this age range.

During acute pyretic disease, water and electrolyte balance may be impaired, causing abnormal serum electrolyte levels (9,10). Serum sodium levels are lower in children that have febrile convulsions than in the normal population (10,11). Also, in febrile convulsions, hyponatremia can be induced by arginine vasopressin released at high levels to affect thermoregulatory neurons through the ventroseptal region of the limbic system for the maintenance of body fluid balance or reduction of fever as an endogenous antipyretic against dehydration which can be associated with fever that occurs in many acute inflammatory events. Children can present with even higher levels of hyponatremia than adults, which results in increased intracellular fluid passage, brain edema, and encephalopathy. Besides, hyponatremia can decrease the amount of intracerebral arterial oxygen (12,13) and lower the seizure threshold (14) by reducing the cerebral blood flow.

Some studies indicate that serum sodium levels are lower in patients with convulsions than that of controls. That is, hyponatremia can increase the risk of recurrence of convulsions in acute pyretic disease (9,15) and the probability of seizure recurrence is higher in the presence of lower sodium levels, which emphasizes the importance of sodium measurement (6). However, some researchers reported no significant difference in sodium levels between recurrent and non-recurrent cases (9, 16) and those suggesting that the sodium level should not be investigated if the seizure recurs within 24 hours (4). The majority of our patients had hyponatremia, which is in agreement with the literature. When the cases without recurrent seizures were evaluated, hyponatremia was detected in 42% of patients at the time. When the cases with recurrent seizures were evaluated, hyponatremia was detected in 52.4% of patients at the time of the first seizure and 61.9 % at the time of recurrence. In recurrent seizures, hyponatremia was slightly more than seizures that nonrecurrent. But there was no significant relationship between recurrence and hyponatremia.

Stress hyperglycemia is a temporary elevation in blood glucose levels as a result of increased catecholamines, cortisol, growth hormone, glucagon, and cytokines during acute stress, and glucose returns to normal ranges when stress is reduced (17). It was reported that those who had seizures for the first time or experienced severe and prolonged seizures had higher stress hyperglycemia. In recurrent seizures, the presence of various conditions, such as increased excitability in fever-sensitive ion channels

and neurons, as well as the possibility of a lower seizure threshold, has been demonstrated. This neuroendocrine response results in excessive gluconeogenesis and glycogenolysis (18,20). The severity of hyperglycemia in response to stress is associated with the intensity of the stressor. Therefore stress hyperglycemia in the acute disease seems to be a marker of disease severity. Stress hyperglycemia present in approximately 5% of children presenting to the emergency service with acute disease. That stress hyperglycemia may be a predictor of recurrence in the first 24 hours in children with febrile convulsions is embraced by some researchers while rejected by others (20).

In the present study, the prevalence of stress hyperglycemia in children with non-recurrent febrile seizure was 23.1%, in children with recurrent febrile seizure was respectively first-last seizure 28.6% - 23.8%. In studies accepting the glucose threshold level of 150 mg/dl to define stress hyperglycemia, the rate of stress hyperglycemia was reported as 10-12.9% (20). Previous studies investigated recurrence within 24 hours, whereas we evaluated it in the late period. Although not statistically significant, the mean glucose level in the recurrent seizure was lower than the first seizure, this finding is consistent with the literature. It suggests that the seizure threshold is lower in recurrences and that seizures can occur even in less stress without the opportunity for cortisol and catecholamines to rise to the point of causing stress hyperglycemia.

CONCLUSION

A recurrent febrile convulsion is more common in boys than in girls. Sodium levels may be low; glucose levels may be high in most patients with febrile seizures. Hyponatremia and hyperglycemia can also occur in recurrent seizures, but this cannot be considered as a predictive marker of seizure recurrence. Severe stress hyperglycemia may develop in children that have had recurrent febrile seizures this situation being lower in the recurrent seizures than the first seizure indicates that the seizure threshold may reduce recurrences. There is a need for prospective studies with more extensive case series to confirm the results.

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REFERENCES

1. Fayyazi A, Khajeh A, Baghbani A. Comparison of Effectiveness of Topiramate and Diazepam in Preventing Risk of Recurrent Febrile Seizure in Children under Age of 2 Years. Iran J Child Neurol 2018;12:69-77.
2. Natsume J, Hamano SI, Iyoda K, et al. New guidelines for management of febrile seizures in Japan. Brain Dev 2017;39:2-9.

3. Graves RC, Oehler K, Tingle LE. Febrile seizures: Risks, evaluation, and prognosis. *AmFam Physician* 2012;85:149-53.
4. Maksikharin A, Prommalikit O. Serum sodium levels do not predict recurrence of febrile seizures within 24 hours; *PaediatrInt Child Health* 2015;35:44-6.
5. Lee JY, Kim JH, Cho HR, et al. Children Experiencing First-Time or Prolonged Febrile Seizure Are Prone to Stress Hyperglycemia. *J Child Neurol* 2016;31:439-43.
6. Agrawal J, Poudel P, Shah GS, et al. Recurrence Risk of Febrile Seizures in Children. *J Nepal Health Res Counc* 2016;14:192-6.
7. Aksay A, Kumandas S, Per H, et al. Demographic characteristics of patients presented to pediatric emergency department with febrile seizure and identification of risk factors for recurrence. *J Dr. Behcet Uz Children's Hospital* 2018;8:159-66.
8. Ojha AR, Shakya KN, Aryal UR. Recurrence Risk of Febrile Seizures in Children. *J Nepal Paediatr Soc* 2012;32:33-6.
9. Kiviranta T, Airaksinen EM. Low sodium levels in serum are associated with subsequent febrile seizures. *Acta Paediatr* 1995;84:1372-4.
10. Nickavar A, Hasanpour H, Sotoudeh K. Validity of serum sodium and calcium screening in children with febrile convulsion. *Acta Medicaliranica* 2009;47:229-31.
11. Heydarian F, Ashrafzadeh F, Kam S. Simple febrile seizures: the role of serum sodium levels in prediction of seizure recurrence during the first 24 hours. *Iran J Child Neurology* 2009;3:31-4.
12. Tarim O. Water Metabolism Disorders. Cinaz P, Darendeliler F, Akıncı A et al. *Pediatric Endocrinology. İstanbul. Nobel medical bookstores* 2014;633-45.
13. Hasegawa H, Okubo S, Ikezumi Y, et al. Hyponatremia due to an excess of arginine vasopressin is common in children with febrile disease. *Pediatr Nefrol* 2009;24:507-11.
14. Hugen CA, Oudesluys-Murphy AM, Hop WC. Serum sodium levels and probability of recurrent febrile convulsions. *Eur J Pediatr* 1995;154:403-5.
15. Nadkarni J, Binaykiya I, Sharma U, et al. Role of serum sodium levels in prediction of seizure recurrence within the same febrile illness. *Neurology Asia* 2011;16:195-7.
16. Thoman JE, Duffner PK, Shucard JL. Do serum sodium levels predict febrile seizure recurrence within 24 hours? *Pediatr Neurol* 2004;31:342-4.
17. Weiss SL, Alexander J, Agus MS. Extreme stress hyperglycemia during acute illness in a pediatric emergency department. *Pediatr Emerg Care* 2010;26:626-32.
18. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; 373:1798-807.
19. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care* 2013;17:305.
20. Lee JY, Kim JH, Cho HR, et al. Children Experiencing First Time or Prolonged Febrile Seizure are Prone to Stress Hyperglycemia. *J Child Neurol* 2016;31:439-43.