

Original paper

The Association between Hyponatremia and Recurrent Febrile Convulsions

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Abstract

Background: Febrile seizures are common pediatric problem, yet there is a great deal of disagreement about the appropriate diagnostic evaluation of a child with this disorder. Different predisposing factors have been suggested to enhance the susceptibility to febrile seizure and its recurrence. Fever play an important role in causing disturbances in fluid and electrolytes balance, hyponatremia has been thought to enhance the susceptibility to seizures.

Objective: To determine the effect of hyponatremia in recurrent febrile convulsions.

Patients And Methods: A case-control study which carried out in Al- Zahraa teaching hospital in Al-Najaf city during the period between 1st of January to end of October 2015. One hundred fifty children were included in this study. We classified the patients into three groups; group (A) included (50) children presented with fever without seizure, group (B); (50) children presented with simple febrile convulsion, group (C); (50) children presented with recurrent febrile convulsions. Group A concenter as control group. The serum level of Na were estimated in these 3 groups by Na kits.

Results: One hundred fifty children were studied with age range between (6months-6years) old. We compare the S. Na among the three groups;

It is found that male in group A represented 26 (52%) and 24 (48%), 28(56%) in group B and C respectively, while female represented by 24 (48%), 26 (52%), 22 (44%) in groups A, B, C respectively, with p value of 0.726.

There were no significant difference between male and female, in all age groups. Also it is shown that family history of febrile convulsion represented 20%, 50%, 50% in group A, B, C respectively, in family history of recurrent febrile convulsion, represented 4%, 4%, 10%, in group A, B, C respectively, and with family history of epilepsy show group A (0%), group B (4%), group C (0%).

While p value in family history of febrile convulsion (0.002), in family history of recurrent febrile convulsion (0.345), in family history of epilepsy (0.132).

So there were no significant difference in all parameters except family history of febrile convulsion which is significant in all three groups, P value=0.002.

Also the study will show no significant difference in age, white blood cell count, and random blood surge while there is significant difference in temperature.

A significant difference in serum sodium level which is lowest in group C. Regarding Calcium level, there is significant difference between group A and B.

Conclusion:- There is a significant association between recurrent febrile convulsion and lower level of serum sodium, in which serum sodium concentration is lowest in those patient with recurrent febrile convulsion.

Keywords: Hyponatremia, simple febrile convulsion, serum sodium

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Introduction

Febrile seizure is a most common form of childhood seizure that occurs in (2-5%) of them ⁽¹⁾. Which represented the most common childhood seizure disorder, exist only in association with an elevated temperature. Evidence suggests, however, that they have little connection cognitive function, so that prognosis for normal neurologic function is excellent with children with febrile seizure ⁽¹⁾. Epidemiologic studies have led to the division of febrile seizure into 3 groups, as follows: -simple febrile seizure - complex febrile seizure- symptomatic febrile seizure. Starting *MMR/MMRV* vaccination earlier may reduce seizure risk. Although described by the ancient Greeks, it was not until this century that febrile seizure were recognized as a distinct syndrome separate from epilepsy. In 1980, a consensus conference at febrile held by the National Institutes of Health described a febrile seizure as ((An event in infancy or childhood usually occurring between three month and five year. Associated with fever, but without evidence of intracranial infection or defined case ⁽¹⁾. It does not exclude children with prior neurological impairment and neither provides specific temp. Criteria nor defines a "seizure".

Another definition from the International League against Epilepsy (ILAE) is "a seizure occurring in childhood after 1 month of age associated with a febrile illness not caused by an infection of the C.N.S, without previous neonatal seizure or previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizure ⁽²⁾.

A febrile seizure is defined by the international as a seizure occurring in association with febrile illness in the absence of C.N.S. infection or acute electrolyte imbalance in children older than 1 month without prior a febrile seizure ⁽³⁾. While according Berg. Febrile

seizure are defined as seizure occurring between (6 months - 6 years) of age ⁽⁴⁾.

Approximately 30-50% of children have recurrent seizures with later episodes of fever ^(5, 6).

The American Academy of pediatrics practice parameter does not recommend S. electrolytes be obtained routinely in evaluation of a child with first febrile seizure unless clinically indicated ⁽⁷⁾. Febrile convulsions divided into the following groups:

Simple febrile seizure: which is characterized by:

- The setting is fever in child aged 6 months to 5 years.
- The single seizure is generalized and lasts less than 15 mins.
- The child is otherwise neurologically healthy and without neurologic abnormality by examination or by developmental history.
- Fever (and seizure) is not caused by meningitis, encephalitis, or any other illness affecting the brain. The seizure is described as either a generalized clonic or a generalized tonic-clonic seizure.

❖ Complex febrile seizure:

- Age, neurologic status before the illness, and fever are the same as for simple febrile seizure.
- This seizure is either focal or prolonged (i.e. > 15 mins), or multiple seizures occur in close succession.

❖ Symptomatic febrile seizure: Age and fever are the same as for simple febrile seizure. The child has a preexisting neurologic abnormality or acute illness

In general the febrile seizure is a unique form of epilepsy that occur in early childhood and only in association with an elevation of temp.

The underlying pathophysiology is unknown, but genetic predisposition clearly contribute to the accruing of this disorder ⁽⁵⁾.

Outcomes of febrile seizures: Children with a previous simple febrile seizure are at increased risk of recurrent febrile

seizures; this occur in approximately one third of cases. Children younger than 12 months at the time of either first simple febrile seizure have about 50% probability of having a second seizure, after 12 months, the probability decrease to 30%. Children who have simple febrile seizure are at an increased risk for epilepsy. The rate of epilepsy by age 25 years is approximately 2.4% which is about twice the risk in general population. Sodium plays a key role in our body. It helps maintain normal blood pressure, support the work of our nerves and muscles, and regulate our body's fluid balance. A normal sodium level is between 135-145 mill equivalents per liter (mEq/L) sodium. Hyponatremia occurs when the sodium in our blood falls below 135-mEq/L. Many possible conditions and lifestyle factors can lead to Hyponatremia, including:- Certain medication:- like diuretics, antidepressants and pain medications. Heart, kidney and liver problems:- like congestive heart failure. Syndrome of inappropriate antidiuretic hormone (SIADH). Chronic, severe vomiting or diarrhea. Drinking too much water, Hyponatremia is a condition that occurs when the level of sodium in our blood is abnormally low. Sodium is an electrolyte, and it helps regulate the amount of water that's in and around cells. In hyponatremia, one or more factors- ranging from an underlying medical condition to drinking too much water during endurance sports- causes the sodium in our body to become diluted. When this happens, our body water levels rise, and our cells begin to swell. This swelling can cause many health problems from mild to life-threatening. Two studies in Europe have demonstrated a relationship between low S.Na. Level and risk of developing recurrent seizure within the same febrile illness. One study by Kiviranta and Airaksineu (1995) reported the Na-levels were significantly lower in children with recurrent febrile seizure as compared with simple febrile convulsion,

without recurrence. They concluded that hyponatremia may increase the risk for multiple seizure during the same febrile illness. Moreover, a prospective study published by Hugen et al. (1995) concluded that the probability of repeated episodes of seizure with the same febrile period appeared to be related to the lower S. Na level⁽⁹⁾. In another study S. Na level in febrile convulsion patient was significantly lower than those obtained in children with fever.

Patients and Methods

This study carried out in Al- Zahraa teaching hospital in Al- Najaf city during a period between 1st of January to end of October 2015. The study was conducted on 150 children with 50 of them were with fever and 50 other were with simple febrile convulsion, the rest 50 children with recurrent febrile convulsion. With age range (6-60) months old. Patient studied were divided into 3 groups. Group A: - which included 50 children presented with fever only, no any other sign. Group B: Included 50 other children unrelated to sex, presented with simple febrile convulsion. Group C: Included 50 children presented with recurrent febrile convulsion. Blood samples about 2 cc, was aspirated under aseptic technique for S.Na. level measurement. All consecutive children admitted in pediatrics hospital in E.U. or out-patient or pediatrics ward fulfilling the following criteria:

Inclusion criteria:

- Children aged between (6-60) months, with febrile seizure (defined as a seizure occur in association with a febrile illness. The setting is fever in child aged 6 months to 5 years.
- The single seizure is generalized and lasts less than 15 mins.
- The child is otherwise neurologically healthy and without neurologic abnormality by examination or by developmental history.

– Fever (and seizure) is not caused by meningitis, encephalitis, or any other illness affecting the brain. In the absence of C.N.S. infection or any other defined causes of seizure).

Exclusion criteria:

- Children with unprovoked seizure.
- Complex febrile convulsion.
- Neurological infection.
- Developmental delay.
- Children with history of birth asphyxia.
- Persistent neurological deficit.
- Children with gastroenteritis or pneumonia.

All children included in the study will be subjected to the following:

Demographic data, seizure details, nature of febrile illness, family history of epilepsy, febrile seizure, temp., at admission & nutrition status will be recorded.

Estimation of S. Na, Ca and R.B.S. were done also.

Study measurements:-

- Take 2 cc of blood, from each child in the tube, put it in the centrifuge for 30 mints to take the serum from the sample.
- Then take 2 test tubes, one for the serum, in which put in about 20 microns from the serum, & 2nd one for the standard tube.
- Added article materials for each tube & mixed together for 30 seconds.
- Put both of these tubes in the centrifuge again for 10 mints, then take the precipitate.
- Take 3 tubes, one for standard, one for test, & one for black.
- Added 1cc from the colored materials for each tube, & stay for 5 mints, then read each tube in spectrophotometer in 490 Nm of length.

- Take each reading of each tube to calculate it in the following formula.

$$\frac{\text{Black tube} - \text{Test tube}}{\text{Black tube} - \text{Standard}} \times 150 = \text{S. Na mmol/L}$$

Black tube – Standard

Statistical analysis was done by using SPSS (statistical package for social sciences) version 20 in which we use chi square test for categorical data and ANOVA test with LSD for numerical data.

We set P value ≤ 0.05 as significant.

Results

Data collected from 150 pt. (78 Male, and 72 Female) were analyzed.

50(33.3%) had fever without convulsion, 50 (33.3%) had simple febrile convulsion, 50(33.3%) have recurrent febrile convulsion. In Table (1) there were no significant difference in all parameters except family history of febrile convulsion which significantly less in children with fever only.

Table (2) shows no significant difference in age, WBC count, and RBS. While there is significant difference in temperature between group B with both group A and C which is lower in group B. Also significant difference in serum sodium level which is lowest in group C. Regarding calcium level, there is significant difference between group A and B.

Table (3) Comparison of F.C. in grope B and C with control grope A showed that sodium levels were significantly not different than control grope.

Table (5) those who had low Na level 6 times more likely to develop recurrent febrile convulsion. Comparison of R.F.C with fever without convulsion, in S.Na. level, there were Significance difference between them .

Table 1. comparison between groups in some demographic parameters.

Variable	Fever (A)	Simple febrile convulsion (B)	Recurrent febrile convulsion (C)	P value
Gender	Male	26(52%)	24(48%)	0.726
	Female	24(48%)	26(52%)	
F. Hx of F.C	10(20%)	25(50%)	25(50%)	0.002
F. Hx of R.F.C	2(4%)	2(4%)	5(10%)	0.345
F. Hx of epilepsy	0(0%)	2(4%)	0(0%)	0.132

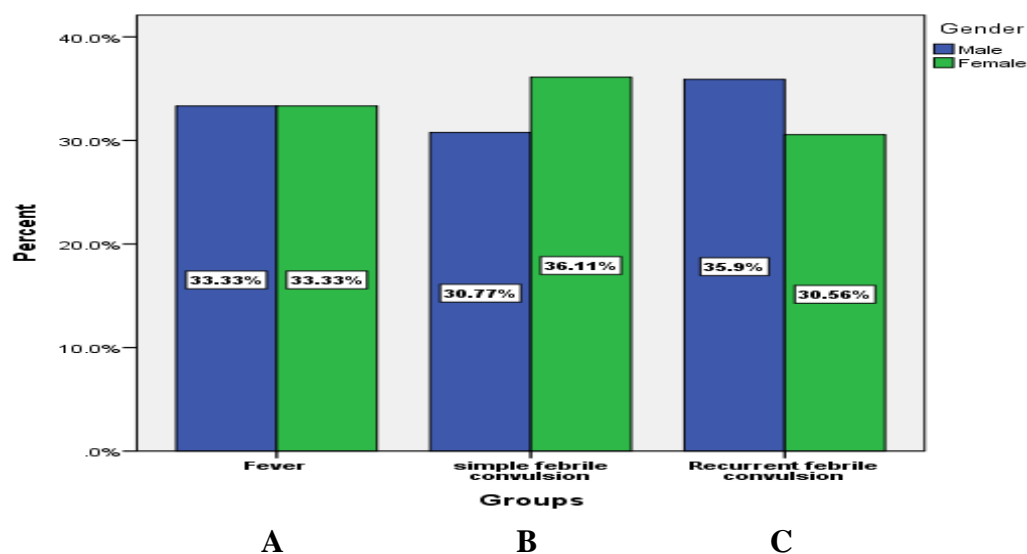


Figure 1. Sex distribution in different groups

Table 2. Comparison between groups in different parameters.

Variable	Fever (A) (n=50)	Simple febrile convulsion (B) (n=50)	Recurrent febrile convulsion (C) (n=50)	P value		
	Mean \pm SD	Mean \pm SD	Mean \pm SD	A versus B	A versus C	B versus C
Age/months	30.82 \pm 18.037	31.38 \pm 15.306	35.43 \pm 14.895	0.862	0.153	0.209
Temprature	38.72 \pm 0.427	38.45 \pm 0.377	38.76 \pm 0.477	0.002	0.634	<0.001
WBC	10640 \pm 2601.09	10534 \pm 3054.71	11080 \pm 3560.1	0.864	0.479	0.379
S.Na	135.18 \pm 1.803	135.10 \pm 2.702	131.76 \pm 3.750	0.893	<0.001	<0.001
S.Ca	8.62 \pm 0.430	8.81 \pm 0.467	8.79 \pm 0.518	0.040	0.068	0.817
RBS	106.98 \pm 11.901	103.90 \pm 12.221	108.38 \pm 12.98	0.215	0.573	0.072

Table 3. Relation between serum Na level and convulsion

	fever with convulsion (n=100)	fever without convulsion (n=50)	p value
hyponatremia	59(59%)	24(48%)	0.201
normal Na level	41(41%)	26(52%)	
odds ratio= 1.559 95% CI=0.745-3.269			

Table 4. Association between serum Na level and simple febrile convulsion

Serum Na	Hyponatremia	Simple febrile convulsion	Groups	P value
	Normal Na level		Fever	
Total		16	24	0.102
		32.0%	48.0%	
		34	26	
		68.0%	52.0%	
			50	
				100.0%
Odds ratio = 0.51 95%CI (0.208-1.241)				

Table 5. Association between serum Na level and recurrent febrile convulsion

	Recurrent febrile convulsion(n=50)	Fever without convulsion (n=50)	p value
hyponatremia	43(86%)	24(48%)	<0.001
normal Na level	7(14%)	26(52%)	
Odds ratio=6.65 95% CI(2.3-19.9)			

Discussion

Febrile convulsion is a terrifying event for the parents, which seeks emergent medical attention. Attempts have been made to identify predisposing risk factors and predictors of seizure recurrent. This knowledge has a practical value whether to admit the child and advising parents of a repeated convulsion⁽⁵⁾.

In current study, we used one hundred fifty child, with mean age (30.82±18.037) in group A, (31.38±15.3306) in group B, (35.43±14.895) in group C, with no significance difference, between male and female, but we found that there is a relationship between hyponatremia and recurrent febrile convulsion, i.e., hyponatremia play as risk factor for recurrent febrile convulsion, p value in A/C <0.001, B/C <0.001 which is significant. Our study was supported by Hugenetal (1995) study consist of age – matched children presented to E.U. with fever, without seizure, and group of healthy afebrile children⁽⁹⁾. Demonstrated a relationship between lower S. Na level and the increase of developing recurrent seizure within the same febrile illness^(8,9) But the study by Kiviranta and Airaksinen's included no control group⁽⁸⁾. Also reported that low S.Na levels played a significant role in recurrent simple febrile seizure. Contradictory to earlier European studies Thoman et al (2004)⁽⁷⁾. In which (175) children ages (6month- 5year) old. Presented with generalize seizure lasting less than 15 mints, to the E.U, in 1999, with reactively revealed, (136) febrile, (39) a febrile as control group, and measure the S.Na levels in all, they found that, the mean S.Na for

the (27) child with >1 febrile seizure 24hour (135.48)mmol/l, didn't differ from those (109), febrile children also seizure didn't recurred with in (24hr) (135.56)mmol/l. This finding may be due to mildly raised ADH during acute febrile infection and, as a result, fluid retention; relative hyponatremia may decrease the threshold of fluids can aggravate hyponatremia and promote febrile seizure⁽¹⁶⁾. And the mean S.Na for 109 children with simple febrile seizure. As well as those were significantly lower than the control group of children with afebrile seizure^(14,15).

Other study in Iran 2009. In which they take a febrile seizure as control

They found that both febrile groups had relative hyponatremia, but with no statistically significant difference between a febrile seizure and febrile seizure.

That is similar to the current study, were we compare between the fever without convulsion and fever with convulsion whether simple or recurrent, we found that it is not significant and p value = (0.201).

While when we compared between fever without convulsion, with recurrent febrile convulsion its significant P value <0.001. However, Iran study similar to the finding of thoman et al. study⁽¹⁴⁾. Study done by MaskiKharin A, etal in Thailand⁽¹⁷⁾.

This study was undertaken in children with febrile seizure from January (2007- Decber- 2011) with retrospective data collected from medical record, they used (315) children with febrile seizure, with mean age (12.5) month, which more than our study 181(57.5%) male, (47) episodes of recurrent febrile seizure within 24hour occurred in 39 children (12.4%) - 276 pt. with single febrile seizure the serum of Na.

was (134.94 mmol/L) and those in whom febrile seizure recurrent within 24hrs (134.99) mmol/L so they found that there were no significant difference. While in our study, there was significant difference between simple febrile convulsion and recurrent febrile seizure in which P value <0.001.

Conclusion

There are many factors that affect the cause the febrile convulsion.

The current study demonstrated that decrease in the level of S.Na or (relative hyponatremia) may play a role as a risk factor for recurrent febrile convulsion. There is a significant association between recurrent febrile convulsion and lower level of serum sodium, in which serum sodium concentration is lowest in those patient with recurrent febrile convulsion.

Recommendation

Because hyponatremia is a risk factor for recurrent febrile convulsion, measurement of serum sodium is recommended in patient with febrile convulsion especially those with recurrent type

References

- Shinnar S. Febrile seizure. In Swaiman KF, Ashwal S, Ferriero DM editor. Pediatric Neurology: principles and practice. 4th ed. Philadelphia: Mosby Elsevier; 2006. p. 1078-86.
- Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League against Epilepsy (editorial). *Epilepsia* 1993; 34: 592-6.
- Waruiru C, Appleton R. Febrile seizures: an update. *Arch Dis Child* 2004; 89: 751-6.
- Berg AT. Are febrile seizures provoked by a rapid rise in Temperature? *Am J Dis Child* 1993; 147: 1101-3.
- Behrman RE, Kliegman RM. Paroxysmal disorders. In: Kliegman RM, Behrman RE, editors. *Nelson Essential of Pediatrics*. 5th ed. Philadelphia: Saunders; 2006. p. 838.
- Johnson MV. Seizures in childhood. Behrman RE, Kliegman RM, Jenson RB, editors. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: WE Saunders; 2004. p. 1993-2009.
- Duffner PK, Baumann RJ. A synopsis of the American Academy of Pediatrics' practice parameters on the evaluation and treatment of children with febrile seizures. *Pediatr Rev* 1999; 20: 285-7.
- Kiviranta T, Airaksinen EM. Low sodium levels in serum are associated with subsequent febrile seizures. *Acta Paediatr* 1995; 84: 1372-4.
- Hugueny CA, Oudesluys-Murphy AM, Hop WC. Serum sodium Levels and probability of recurrent febrile convulsions. *Eur J Pediatr* 1995; 154: 403-5.
- Chiarelli F, De Palma C, Verrotti A, Lombardi G, Domizio S. Electrolytic changes in febrile convulsions. *Pediatr Med Chir* 1985; 7: 249-52.
- Pal DK, Kugler SL, Mandelbaum DE, Dumer M. Phenotypic features of familial febrile seizures: case-control study. *Neurology* 2003; 60: 410-4.
- Berg AT, Shinnar S. Complex febrile seizures. *Epilepsia* 1996; 37: 126-33.
- Berg AT, Shinnar S, Darefsky AS, Holford TR, Shapiro ED, Salomon ME, et al. Predictors of recurrent febrile seizures. A prospective cohort study. *Arch Pediatr Adolesc Med* 1997; 151: 371-8.
- Thoman JE, Duffner PK, Shucard JL. Do serum sodium Levels predict febrile seizure recurrence within 24 hours? *Pediatr Neurol* 2004; 31: 342-4.
- Miceli Sopo, Cuomo B, Federico G, Avantagegiat OMD, Pugliese A, Navarra PL, et al. In vivo and in vitro production of interleukin-1 alter Febrile convulsions. *Pediatr Med Chir* 2001; 23: 87-7.
- Virta M, Hurme M, Helminen M. Increased plasma levels of pro- and anti-inflammatory Cytokines in patients with febrile seizures. *Epilepsia* 2002; 43: 920-3.
- A. Maskikharin and O. Prommalkit, Serum sodium levels do not predict recurrence of febrile seizures within 24 hours, 2015; 35: 44-46.