Relation between Febrile Seizure Recurrence and Hyponatremia in Children: A Single-center Trial

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Background: Febrile seizure (FS) is one of the most common types of seizure in pediatrics. Objective: The aim of this study was to compare serum sodium in children with simple or recurrent FS and seizure without fever. Materials and Methods: This was a cross-sectional prospective study conducted between September 2015 and April 2017 in patients aged between 6 months and 6 years, who were admitted to a tertiary educational medical center in the north of Iran. Patients were categorized into three groups, group A: simple FS, group B: recurrent FS, and group C: afebrile seizure. Serum sodium level was measured on admission and/or when the seizure occurred. Results: The study included 248 patients aged 6 months to 6 years. Their mean age was 22.38 ± 1.34 months. Hyponatremia was found in 6% of group A, 7.5% of group B, and 6% of group C. The mean sodium level in group A (134.46 ± 2.3 mEq/L) and group B (134.35 ± 2.06 mEq/L) did not disclose meaningful difference, but it was significantly lower in febrile groups than in the control group. Conclusion: Although the results did not show that the lower level of serum sodium increased the risk of seizure recurrence during the next 24 h in febrile illness, lower serum sodium concentration was more common in FS groups.

Keywords: Children, complex, febrile, hyponatremia, recurrence, seizure, sodium

INTRODUCTION

The seizure is one of the most common diseases of childhood that occurs in 4%–10% in pediatrics and adolescence.[1] It may be provoked with fever in children, called as febrile seizure (FS). This condition is defined as the seizure in a febrile 6- through 60-month-old children in the absence of intracranial infections or other metabolic disturbances.[2] FS is the most common type of seizure disorders in children, affecting 2%–5% of children.

The Quality Standards Subcommittee of the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society recommended electrolyte evaluation for new-onset seizure in pediatrics based on clinical sign and symptom.[3] The role of serum sodium (SNa) disturbance, especially hyponatremia, in provoking seizures in children and neonates is well known.[4-8] The concentration of SNa is influenced by many factors, such as free water intake, secretion of the antidiuretic hormone (ADH), body water, urinary loss, and underlying diseases.[9]

In addition to the patient’s baseline condition or diseases that may induce hyponatremia, iatrogenic interventions such as administration of hypo-osmolar fluids may cause in-hospital hyponatremia that potentially may lead to complications of central nervous system.[10-13] Regarding the definite effect of SNa on neurological activities in addition to nonconclusive evidence on the importance of SNa in FS and the lack of enough studies

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in this field, the aim of this study was to compare SNa concentration in children with simple or recurrent FS and seizure without fever.

**Materials and Methods**

This was a cross-sectional prospective study conducted between September 2015 and April 2017, in patients aged between 6 months and 6 years, who were admitted to the pediatric service in a tertiary educational medical center in the north of Iran.

The study protocol was approved by the institutional ethics committee with approval number IR.MAZUMS.REC.1395.2956, and the written informed consent was obtained from the parents of all patients before enrollment.

The patients admitted for generalized seizure were eligible for inclusion in the study when they were between 6 months and 6 years of age and their seizure lasted less than 15 min. The exclusion criteria were a history of intravenous fluid therapy in the previous 48 h, failure to thrive,[14] malabsorption, meningitis, encephalitis, previously known renal disease, brain tumor, renal dysfunctions, head trauma, and developmental delay.

The patients who had a history of previous afebrile seizure were also excluded. The patients were categorized into three groups, group A: simple FS, group B: recurrent FS in the next 24 h after the first seizure, and group C: afebrile seizure as the control group.

Patients’ gender, age, history for seizure in first-degree relatives, temperature, seizure duration, seizure repetition, and the most probable cause of fever were documented.

SNa was measured on admission and/or when the seizure occurred. Hyponatremia was defined as SNa below 135 mEq/L.

Length of stay in hospital (LOS) was calculated by subtracting the day of admission from the day of discharge.

**Statistical analysis:** The collected data were analyzed by the Statistical Package for the Social Sciences (SPSS) software, version 16, SPSS Inc. Chicago, USA. Chi-square test and t test were applied to draw the inferences. The results were statistically significant when \( P < 0.05 \).

**Results**

The study included 248 patients aged 6 months to 6 years. Their mean age was 22.38 ± 1.34 months, the mean seizure duration was 6.45 ± 3.2 min, and the most common seizure was generalized tonic–clonic (GTC) in febrile groups, 92% [Table 1].

The cases were allocated to three separate groups: group A, children who had simple FS \((n = 132)\), group B, who had recurrent FS in the first 24 h \((n = 66)\), and group C (control group), who had an afebrile seizure \((n = 50)\). Demographic characteristics of these groups were shown in Table 1. Of the febrile cases, 33.3% had recurrent FS, and of the total cases, 20.1% were afebrile.

Although males were somewhat dominant in all groups, no significant difference was observed. Albeit, seizure duration was different in group A and B \((P = 0.001)\), it must be kept in mind that the sources of history for seizure duration were parents or other relatives in the majority of cases.

The mean of temperatures was not different in febrile groups. In the FS groups \((A \text{ and } B, n = 198)\), 132 (66.6%) patients used acetaminophen or nonsteroidal anti-inflammatory drugs before seizure to control the fever.

### Table 1: Demographic characteristics of three groups

| Variable                        | Group A \((n = 132)\) | Group B \((n = 66)\) | Group C \((n = 50)\) | \(P\) value   |
|---------------------------------|------------------------|-----------------------|-----------------------|---------------|
| Age months                      | 22.27 ± 1.24           | 23.19 ± 1.12          | 21.69 ± 1.8           |               |
| Male (%)                        | 73 (55.3)              | 39 (59)               | 28 (56)               |               |
| Temperature (°C)                | 38.52 ± 0.52           | 38.56 ± 0.5           | No data               |               |
| Seizure duration (minutes)      | 5.4 ± 2.64             | 7.5 ± 4.13            | No data               |               |
| Positive family history for febrile seizure (%) | 28 (21)                | 17 (25)               | 9 (18)                |               |
| Positive family history for convulsion (%) | 12 (9)                 | 8 (12)                | 5 (10)                |               |
| Hospital stay (day)             | 1.4 ± 1.3              | 2.8 ± 1.7             | No data               |               |

**Group A vs. B, 0.000**

**Group A vs. C, 0.014**

**Group B vs. C, 0.000**

**Group A vs. B, 0.418**

**Group A vs. C, 0.269**

**Group B vs. C, 0.739**

**Group A vs. B, 0.72**

**Group A vs. B, 0.001**

**Group A vs. B, 0.47**

**Group A vs. C, 0.035**

**Group B vs. C, 0.323**

**Group A vs. B, 0.5**

**Group A vs. C, 0.851**

**Group B vs. C, 0.721**

**Group A vs. B, 0.034**
The percentage of positive family history for FS in groups A, B, and C was 21%, 25%, and 18%, respectively. The difference between simple FS group and the afebrile group was statistically significant, \( P = 0.035 \). Family history for convulsion in simple FS group was 9%, in recurrent FS group, 12%, and in the control group, 10%, and no significant difference was observed between groups [Table 1].

The mean LOS in the febrile groups (A and B) was \( 2.7 \pm 1.6 \) days in total. Hospital stay in the recurrent FS group was longer, \( P = 0.034 \).

The main cause of fever in febrile groups was upper respiratory infection followed by gastroenteritis, fever without a localized sign, and acute otitis media [Table 2].

Hyponatremia was found in 6% of simple FS group, 7.5% of recurrent FS group, and 6% of afebrile seizure group, the intergroup comparison did not show a significant difference in the occurrence of hyponatremia. Figure 1 shows the range of SNa in three groups.

The most common type of seizure was GTC in groups A and B. Although comparison of mean SNa level in simple FS (134.46 \( \pm \) 2.3 mEq/L) and recurrent FS groups (134.35 \( \pm \) 2.06 mEq/L) did not disclose meaningful difference (\( P = 0.333 \)), SNa level was significantly lower in febrile groups (A and B) than that in the control group (\( P < 0.001 \)) [Table 3].

**DISCUSSION**

The main objective of this study was to compare SNa levels in children with simple FS or recurrent FS in the next 24 h after first seizure with those children having afebrile seizure.

Surprisingly, despite the prevalence of electrolyte abnormalities in pediatric seizure, less scientific literature was focused on it.\(^{[15]}\) Compared to previous prospective studies, the sample size in our study was larger, and we used a control group consisting of patients with afebrile seizure.

Despite the fact that previous studies affirm SNa level as a predictor for seizure recurrence,\(^{[16,17]}\) in our study, the SNa level was not different in FS groups with or without a recurrent seizure. The results of a study by Thoman et al.\(^{[18]}\) as well as the results of our study reported that there was no difference between SNa levels in recurrent FS versus simple FS group.

The findings of a study by Thoman et al.\(^{[18]}\) which were similar to our findings, reported that SNa level in FS groups—with or without seizure recurrence—was significantly lower than SNa level in the group with the seizure but without fever.

Although the American Academy of Pediatrics (AAP) did not recommend to evaluate serum electrolyte in simple FS routinely, they suggested obtaining appropriate histories and performing careful physical examinations to identify cases who needed electrolyte evaluation. Similar to our findings, the AAP noted that children with FS have relatively low SNa concentration.\(^{[19]}\)

The occurrence of complex febrile seizures reported from 9% to 37% in the children admitted for their first febrile seizure.\(^{[16,20,21]}\) As a criterion for complex FS, we found that 33% of all first FS had a recurrent seizure in the first 24 h after initial seizure.

On the basis of the fact that hospital duration of seizure was obtained from parents or caregivers’ reports, we could not independently confirm the timing of seizures, which occurred out of the hospital.

![Figure 1: Maximum, mean, and minimum of serum sodium concentration in three groups](image)

### Table 2: Causes of fever

| Causes                        | Group A (\( n = 132 \)) | Group B (\( n = 66 \)) |
|-------------------------------|-------------------------|------------------------|
| Upper respiratory infection (%) | 54 (40.9)              | 25 (37.8)              |
| Acute otitis media (%)        | 17 (12.8)              | 8 (12.1)               |
| Gastroenteritis (%)           | 21 (15.9)              | 11 (16.6)              |
| Fever without localized sign (%) | 19 (14.3)          | 10 (15.2)              |
| Urinary tract infection (%)   | 14 (10.6)              | 6 (9.1)                |
| Vaccination (%)               | 4 (3)                  | 2 (3.1)                |
| Other (%)                     | 3 (2.5)                | 4 (6.1)                |

### Table 3: Serum sodium concentration on admission

| Group of seizure types | Mean serum sodium ± SD (mEq/L) | \( P \) value |
|-----------------------|---------------------------------|--------------|
| Group A               | 134.46 ± 2.3                    | Group A vs. B, 0.333 |
| Group B               | 134.35 ± 2.06                   | Group A vs. C, <0.001 |
| Group C               | 137.05 ± 2.82                   | Group B vs. C, <0.001 |

SD = standard deviation
Similar to other studies, the generalized seizure was the most frequent type of FS in our study,[19,22] and the most common seizure in the age-group of 6 through 60 months was the FS (80%).

In some studies reported that seizure occurrence in pediatric from 1 month to 5 years old is higher in boys than girls,[17,21,22] in this study, we also found that 56% of seizures occurred in male in all cases as well as male superiority in separated groups.

Muzafar et al.[22] found 7.7% hyponatremia in cases of acute symptomatic seizures. Although we excluded cases of acute symptomatic seizures, overall hyponatremia was found 6% in our study in patients who had a seizure with or without fever.

Positive family history for FS was reported from 25% to 40% in literature.[23] In our study, 33% and 38% of patients in simple FS group and recurrent FS group, respectively, had a family history of FS.

**Limitations**: We excluded some patients who had strong risk factors for hyponatremia such as head trauma or meningitis. The level of ADH was not measured, whereas inappropriate elevated ADH secretion is a well-known problem in pediatric practice that could cause hyponatremia. In spite of the fact that this study was large enough for the purpose, a larger study will lead to more accurate results.

FS is the most common type of seizure in the children aged 6 through 60 months. Lower SNa level is more common in FS with or without recurrence in the first 24 h after the first seizure compared to that in afebrile seizure.

The results did not show that the lower level of SNa increased the risk of seizure recurrence during the next 24 h in febrile illness. Thus, in the FSs, we recommend evaluation of SNa level based on predisposing factors and clinical signs and symptoms.

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**Conflicts of interest**
There are no conflicts of interests.

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