

Assessment of serum sodium levels among the febrile seizures children in a tertiary care hospital

V Bharathi Tulasi Penta¹, Lakshmi Lakkappa²

From Senior Resident, Department of Pediatrics, ¹St. Johns Medical College, Bengaluru, ²Chamarajanagar Institute of Medical Sciences, Chamarajanagar, Karnataka, India

Corresponding to: Dr. Lakshmi Lakkappa, Senior Resident, Department of Paediatrics, Chamarajanagar Institute of Medical Sciences, Chamarajanagar, Karnataka, India. E-mail: statisticsclinic2018@gmail.com

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ABSTRACT

Background: Pathophysiology of febrile seizures (FS) remains unclear. During acute febrile illness, mild disturbances of water and electrolyte balance occur frequently, particularly hyponatremia, which might predispose the child to convulsions. **Objective:** The objective of the study was to assess the serum sodium levels among the children with FS in a tertiary care hospital. **Materials and Methods:** A prospective case-control study was conducted at a tertiary care hospital in Bengaluru from January 2014 to October 2016. A total of 80 children with febrile convulsions were taken as cases and 80 children admitted for other causes were taken as controls. Serum sodium levels were estimated and compared. **Results:** Mean age of cases was 20.09 ± 11.63 months while that of the controls was 20.08 ± 13.1 months. Among cases, 28.7% had hyponatremia, 66.2% had normal sodium levels, and 5% had hypernatremia. In controls, hyponatremia, normal sodium levels, and hypernatremia were seen in 6.2%, 82.5%, and 11.2% children, respectively. **Conclusion:** Incidence of hyponatremia was significantly high among the children with FS when compared to the controls. The mean serum sodium levels in cases were significantly lower than that in controls suggesting the role of relatively low serum sodium levels in the occurrence of FS in children.

Key words: Electrolytes, Febrile seizures, Hyponatremia, Seizure

Febrile seizure (FS) is the most common form of seizures in pediatrics. They are generally not associated with high morbidity or mortality but are very frightening for parents and lead to frequent emergency department admissions [1]. Nearly 2–5% of children experience FS, most of them being simple (65–90%) [2]. The incidence of FS varies depending on the geographic location, with higher prevalence found in Japan [3]. Although earlier Indian studies suggested that up to 10% of children experience a febrile seizure, recent data indicate that the incidence in India is similar to that reported from the west [4]. Approximately 30–50% of children have recurrent seizures with subsequent episodes of seizures. The peak incidence of FS occurs in the 2nd year of life and is more common in males [5].

Pathophysiology of FS remains unclear; it is suggested that FS is an age-dependent response of the immature brain to fever, as studies in animal models have suggested that during the brain maturation process, there is enhanced neuronal excitability [4]. During acute febrile illness, mild disturbances of water and electrolyte balance occur frequently, particularly hyponatremia, which might predispose the child to convulsions [6,7].

In general, there is an increase in total body water during the febrile period that diminishes during convalescence. Fluid conservation during fever occurs in parallel with an increase in the thirst threshold. Other factors influencing the fluid balance,

and thus the degree of fluid conservation, include diarrhea, vomiting, and respiratory infections, and rhinorrhea. In such circumstances, there may be loss of electrolyte-rich fluids, which prompted an increase in the extent of fluid conservation depending on the severity of the loss. Oral or intravenous replenishment with hypotonic fluids not only can restore the lost water but can also exacerbate the deficit in electrolytes [8]. Hyponatremia has been reported in patients with diverse acute infections such as dengue, rotavirus gastroenteritis, encephalitis, meningitis, septicemia, bronchiolitis, pneumonia, severe acute respiratory syndrome, severe malaria, as well as a variety of other non-specific infections [8].

Among the electrolytes, sodium is an important factor in neuronal cell depolarization and production of electrical discharge and finally seizures [9]. Even in animals, reduced serum sodium levels have been shown to lower the threshold to convulsive stimuli. No study to date has demonstrated a benefit for antipyretic use (either acetaminophen or ibuprofen) in decreasing the incidence or recurrence of FS. This suggests that fever is not the only factor involved in the etiology of FS. However, American Academy of Pediatrics (AAP) does not recommend other routine blood evaluations to identify the cause of simple FS, that is, serum electrolytes, calcium, phosphate, magnesium, hemogram, or blood glucose, and unless clinically indicated [10].

Although AAP does not recommend serum sodium evaluation in these children, some researchers found serum sodium levels to be lower in children with multiple seizures within the same febrile illness during routine electrolyte studies in patients with FS. Controversies exist regarding the role of relative hyponatremia in the prediction of FS and its recurrence within the first 24 h. Considering the contradictory reports and the importance of pediatric FSs and their possible recurrence within the first 24 h, we conducted this prospective study to investigate the role of serum sodium in FS. If relative hyponatremia is predictive of seizure recurrence in the same febrile illness, sodium replacement and fluid restriction might be indicated in selected patients.

MATERIALS AND METHODS

A case-control prospective study was undertaken in the department of pediatrics, in a tertiary care hospital in Bengaluru from January 2014 to October 2016. Sample size was estimated using the mean serum sodium levels between cases and controls as 135.4 ± 4 mmol/L and 137.94 ± 2.92 mmol/L. Using these values at 95% confidence limit and 80% power, a sample size of 30 was obtained in each group. With 10% non-response, a minimum sample size of $30 + 3 \approx 33$ subjects was considered for each group.

After obtaining the Institutional Ethical Committee clearance, all the children aged between 6 months and 5 years with FS being admitted during the study period were included as “cases.” Cases were classified into simple FS and atypical/complex FS/febrile status epilepticus (FSE). If a child had multiple episodes of seizures without fully regaining consciousness between them, the seizures were counted as a continuous one, that is, FSE. When the child had a history of FS in the past, that child was considered to have recurrent FS. Equal number of children aged between 6 months and 5 years with febrile illness and without seizures being admitted during the study period was included as “controls.” Those patients with afebrile seizures, neurological infections, developmental delay, children with a history of birth asphyxia, persistent neurological deficit, children with severe dehydration, and children found to have delayed milestones or afebrile convulsions on follow-up during the study period, were excluded from the study.

Detailed demographic profile, clinical history, physical examination findings, and laboratory findings were collected using a semi-structured questionnaire. Children included in the study were subjected to estimation of serum sodium at the time of admission. 2 ml of blood sample was collected in unheparinised tube and sent for estimation of serum sodium which was interpreted by ion-selective electrode method in an electrolyte analyzer (AVL9180, make SENSACORE health care and diagnostic products). Sodium values <135 mmol/L were considered hyponatremia, 135 – 145 mmol/L was considered normal, and values >145 mmol/L were considered hypernatremia. Data were entered into the excel sheet and analyzed using SPSS version 22 software.

RESULTS

The study included 80 subjects in both case and control group and analyzed as below. Mean age of cases was 20.09 ± 11.63 months while that of the controls was 20.08 ± 13.1 months. However, there was no significant difference in age and sex distribution between the two groups (Table 1). In this study, 82.5% (66) cases had simple seizures and 17.5% (14) had atypical seizures. In children with atypical FS, 1 child had focal seizures, 3 children presented with FSE, and 10 children had multiple seizures during the same febrile illness. Total 75% (60) children had 1st episode of seizure and 25% (20) had recurrent seizure.

Among cases, 28.7% (23) had hyponatremia whereas among controls, only 6.2% (5) had hyponatremia and this difference was statistically significant ($p < 0.001$). However, the mean sodium levels among the cases were 137.5 ± 4.5 and that among controls were 140.9 ± 3.7 (Table 2).

Among children with simple FS, 24.2% (16) had low sodium whereas, among those who had multiple seizures in the same febrile illness, 60% (6) had hyponatremia. Mean sodium level among children with multiple seizures in same febrile illness was 136.5 ± 6.2 mmol/L compared to children with single episode (137.7 ± 4.1 mmol/L); however, the difference was not statistically significant (Table 3).

The mean sodium level among children with recurrent FS was higher than with the first episode of FS, but this difference was not statistically significant (Table 4).

Table 1: Demographic characteristics of the study participants

Parameter	Cases n=80 (%)	Controls n=80 (%)	p value
Age groups (years)			
<1	23 (28.8)	32 (40)	$\chi^2=5.225$, df=4, p=0.265
1–2	41 (51.2)	27 (33.8)	
2–3	9 (11.2)	13 (16.2)	
3–4	3 (3.8)	4 (5)	
4–5	4 (5)	4 (5)	
Age, mean $\pm$ SD (months)	20.09 $\pm$ 11.63	20.08 $\pm$ 13.1	0.995
Sex			
Male	50 (62.5)	48 (60)	0.746
Female	30 (37.5)	32 (40)	

SD: Standard deviation

Table 2: Comparison of serum sodium levels among cases and controls

Laboratory values	Group		p value
	Cases	Controls	
	n (%)	n (%)	
Serum sodium (mmol/L)			
Hyponatremia	23 (28.7)	5 (6.2)	$\chi^2=14.91$, df=2, p=0.001*
Normal sodium	53 (66.2)	66 (82.5)	
Hypernatremia	4 (5.0)	9 (11.2)	
Serum sodium at admission mean $\pm$ SD	137.5 $\pm$ 4.5	140.9 $\pm$ 3.7	<0.001*

SD: Standard deviation

Table 3: Comparing sodium levels among simple FSs and multiple seizures in the same febrile illness

Type of seizure	Simple seizure (%)	Multiple seizures in the same febrile illness	p value
Serum sodium (mmol/L)			
Hyponatremia	16 (24.2)	6 (60.0)	$\chi^2=1.545$, df=2, p=0.461
Normal sodium	46 (69.7)	4 (40.0)	
Hypernatremia	4 (6.1)	0 (0.0)	
Serum sodium at admission (mean $\pm$ SD)	137.7 $\pm$ 4.1	136.5 $\pm$ 6.2	0.429

FS: Febrile seizure, SD: Standard deviation

Table 4: Comparing sodium levels among children with first episode of febrile seizures and recurrent febrile seizures

Episodes of seizure	1 st episode	Recurrent	p value
Serum sodium			
Hyponatremia	21 (35.0)	2 (10.0)	$\chi^2=4.67$, df=2, p=0.097
Normal sodium	36 (60.0)	17 (85.0)	
Hypernatremia	3 (5.0)	1 (5.0)	
Serum sodium at admission (mmol/L) mean $\pm$ SD	137.0 $\pm$ 4.6	139.0 $\pm$ 3.6	0.074

FS: Febrile seizure, SD: Standard deviation

DISCUSSION

FS is the most common seizure disorder in childhood, affecting 2–5% of children between the ages of 6–60 months [6]. There have been many studies on the risk factors associated with FS. However, studies evaluating the role of serum sodium in the occurrence of simple FS/multiple FS during the same febrile illness and recurrent FS have shown conflicting results. This study was carried out to find the association between serum sodium levels with the occurrence of FS (single episode and multiple episodes during the same febrile illness and recurrence of FS).

Among the 80 cases enrolled in our study, 14 had atypical FS and 20 had recurrent FS, based on their respective definitions [11]. In our study, cases had significantly higher incidence of hyponatremia than the controls, that is, 28.7% versus 6.2% (p=0.001). Similar results with significantly higher incidence of hyponatremia in children with FS group was reported in two other studies, that is, Hugen *et al.* [12] and Park *et al.* [13] reported an incidence of 52% versus 13% and 44% versus 3% (children with FS vs. febrile controls), respectively.

In the study done by Park *et al.* [13], the incidence of hyponatremia was 31% and 59% in children with simple FS and multiple FS in the same febrile illness, respectively, while

in our study, it was 37% and 56% in children with 1st episode of FS and recurrent FS, respectively. Their results were similar to the results of our study in all the sub-groups except for the recurrent FS group. The number of children with recurrent FS in their study was nearly double the number in our study, which probably is the reason for this difference. Kiviranta *et al.* have also reported hyponatremia in 47% of children with multiple FS in the same febrile illness [2]. The results in both these studies were statistically significant, unlike our study.

In a retrospective analysis done by Rutter and O'Callaghan *et al.* on children admitted with FS, it was found that significant proportion of children with hyponatremia had developed further convulsions during the same febrile illness when compared to children with normal serum sodium at presentation (5/50 vs. 2/113) [14].

The mean serum sodium of the cases in our study was 137.5 $\pm$ 4.5 mmol/L which was significantly lower than that of controls (140.9 $\pm$ 3.7 mmol/L). Similar results were seen in few other studies [4,8,9,13-16] which signify that relative low sodium levels are associated with increased occurrence of FS. Among these studies, 4 studies had controls which included children with fever without convulsions like our study [4,9,13,16] while 3 other studies had selected children with afebrile seizures as controls [8,15-17]. In the prospective case-control study by Park *et al.*, the mean serum sodium was 134.9 $\pm$ 2.3 mmol/L, which was significantly lower than controls (138.2 $\pm$ 2.4 mmol/L) [13]. In an

Indian study done by Sharawat *et al.* [4], (n=70 in each group), the mean serum sodium in cases was 138.2 ± 3.1 mmol/L which was significantly lower than that of controls (142.7 ± 3.8 mmol/L), ($p < 0.01$). Sakha *et al.* [9] have done a prospective case-control study and reported that the mean serum sodium was significantly lower in the cases than in the controls (135.4 ± 4 mmol/L vs. 137.94 ± 2.92 mmol/L; $p < 0.01$) [9]. A prospective case-control study done by Chiarelli *et al.* has also reported the same [16].

In the studies done by Heydarian *et al.*, Kaneko *et al.*, and Thoman *et al.*, the controls were children with afebrile convulsions while we had febrile children without convulsions in our control group [8,15]. Kaneko *et al.* reported mean serum sodium of 134.9 in children with FS which was significantly lower than that in children with afebrile seizures (137.6) ($p < 0.001$) [8]. In retrospective study by Thoman *et al.*, the mean serum sodium in the FS group was significantly lower than the afebrile seizures group [15]. Heydarian *et al.* [17] reported the mean serum sodium levels to be 133.39 ± 10.5 mmol/L, 134.4 ± 4.05 mmol/L, and 136.5 ± 4.13 mmol/L in children with simple FS (n=155), atypical FS (n=61), and afebrile seizures (n=50), respectively. There was disparity among the number of subjects enrolled in each group and choice of controls when compared to our study. Choosing children having afebrile seizures as controls are inappropriate.

There were four studies [5,15,18,19] stating that serum sodium levels do not predict further seizures in children with FS during the same febrile illness, while 4 others [2,10,12,13] showed an opposite result. In a retrospective study done by Thoman *et al.* [15], there was no significant difference in the serum sodium levels between single FS and multiple FS during the same febrile illness groups (135.56 ± 2.42 mmol/L vs. 135.48 ± 2.03 mmol/L). The other retrospective study done by Kenney *et al.* [19] showed no difference in mean serum sodium levels of children with FS whether they had one episode or multiple episodes of seizures during the illness. Fallah and Islami [5] in their prospective study reported mean serum sodium levels to be 137 ± 4.07 mmol/L in children with 1st episode of FS while it was 136.55 ± 4.01 mmol/L in children with multiple FS in the same febrile illness. The difference was not statistically significant.

Hugen *et al.*, Kiviranta and Airaksinen *et al.*, Park *et al.*, and Nadkarni *et al.* in their prospective case-control studies found out that relative hyponatremia was associated with increased risk of multiple seizures during the same febrile illness [2,10,12,13]. The children with recurrent FS in our study had mean serum sodium levels higher than those of children with 1st episode of FS, that is, 139.0 ± 3.6 mmol/L versus 137.0 ± 4.6 mmol/L, with no statistically significant difference, was noticed.

CONCLUSION

The hyponatremia was found to be significantly high among the children with FS when compared to the controls. The mean

serum sodium levels of cases were significantly lower than that of controls suggesting the role of relatively low serum sodium levels in the occurrence of FS in children. There was no significant difference in mean serum sodium levels and the incidence of hyponatremia in children with recurrent FS than in children with 1st episode of FS. Hence, we could not find the definitive role of serum sodium in predicting the recurrence of FSs in subsequent febrile episodes.

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