

Serum Sodium Status in Children with Simple and Complex Febrile Seizure: A Comparative Hospital Based Study

Sunanda Shil^{1*} Mitra Datta¹ Dazy Barua¹ Rifat Jahan²
Prashanta Kumar Shil³ Aparup Kanti Das¹ Rivu Raj Chakraborty⁴

ABSTRACT

Background: Fever is the most common cause of convulsions, in infancy and childhood. Complex febrile seizures are associated with an increased risk of subsequent epilepsy. The present study aimed to evaluate the role of serum sodium levels and associated factors in children with simple and complex febrile seizures admitted to a tertiary level hospital in Bangladesh.

Materials and methods: Children aged between 6 months to 60 months with febrile seizures, admitted to the Paediatric ward of Chittagong Medical College Hospital, Chattogram, were recruited in the study. Serum sodium level at admission were estimated and patients were categorized into two group: simple and complex febrile seizure. Data were analyzed by comparing different variables between two groups.

Results: A total of 60 children were enrolled in the study in which 36 were diagnosed with simple febrile seizures and 24 of them with complex febrile seizures. The mean age was 22.3 months and there was male preponderance with a male to female ratio of 2.3:1. The mean serum sodium level was 136.9 ± 6.5 mmol/l and 18 (30%) patients had hyponatremia. Serum sodium levels were significantly lower in children with complex febrile seizure (134.0 ± 6.1 and 138.9 ± 6.0 , $p=0.003$) than the children with simple seizure. The optimal cutoff value of serum sodium level was 134 mmol/L with an area under the receiver operating characteristic curve of 0.723 (95% CI: 0.590-0.856), with sensitivity of 80.0% and specificity of 50.0%.

Conclusions: Our study suggested that serum sodium levels were significantly lower in children with complex febrile seizures. However, because of its lower specificity value, further studies are needed to confirm the utility of serum sodium level in childhood febrile seizure.

Key words: Complex febrile seizure; Hyponatremia; Serum sodium.

Introduction

Febrile Seizures (FS) which The International League Against Epilepsy defines as seizures that occur in children since their early infantile age because of fever and are not related to the central nervous system causes, are the most common form of childhood seizures.¹⁻³ These seizures are classified into two subgroups: simple febrile seizures consist of a generalized tonic-clonic seizure lasting less than 15 minutes which

does not recur within 24 hours, and complex febrile seizures which last longer than 15 minutes or recur within 24 hours or are focal or have post-ictal paralysis.⁴ Complex febrile seizures represent 20% to 30% of all febrile seizures, and children with complex febrile seizures have a 5-fold increased risk of developing epilepsy.⁵ So, children with complex febrile seizures should be identified separately from those with simple febrile seizures. Predicting seizure recurrence during the same febrile illness might be valuable in advising parents or carers of the risk of repeated seizures.

During an acute febrile disease, mild disturbance of water and electrolyte balance occurs frequently.⁶ Serum sodium levels in children with febrile seizures are lower than in the normal population and if they fall below 120 mmol/L, neurological symptoms such as seizures or alternation of consciousness can occur.⁷⁻⁹ In some cases, this might relate to administration of hypotonic fluids either before or after admission or to poor appetite during the illness. If hyponatremia is confirmed as a risk factor for complex febrile seizure, this would have potential impact on the approach to these patients. Several studies have shown that relative hyponatremia

1. Assistant Professor of Pediatrics
 Chittagong Medical College, Chattogram.

2. Assistant Professor of Pediatric
 Sheikh Hasina Medical College, Tangail.

3. Assistant Professor of Medicine
 Abdul Malek Ukil Medical College, Noakhali.

4. Assistant Professor of Surgery
 Rangamati Medical College, Rangamati.

*Correspondence : **Dr. Sunanda Shil**
 Cell : +88 01716 23 58 89
 Email : sunandashil@gmail.com

Date of Submission : 10th April 2023

Date of Acceptance : 26th May 2023

can predict recurrent febrile seizures during febrile illness.¹⁰⁻¹⁵ However, other studies have demonstrated that serum sodium levels do not predict recurrent seizure during the same febrile episode.¹⁶⁻²⁰ To help in resolving this controversy, this study evaluated the serum sodium levels and the associated factors in children with simple and complex febrile seizures within 24 hours of hospitalization.

Materials and methods

A hospital-based cross-sectional study was conducted at the Department of Pediatrics of Chittagong Medical College Hospital, Chattogram, from May-November 2020. The ethical review committee of Chittagong Medical College approved the study protocol and written informed consent was obtained from the parents or carers of the patients.

Children with first febrile seizures, age group between 6 months - 60 months, were included in the study. Febrile seizures were pre-defined using the standard definition of a seizure accompanied by fever (38°C), without evidence of central nervous system infection, that occurs in infants and children between the ages of 6-60 months with normal neurological development.² Children with neurodevelopmental delay, Meningitis, encephalitis, Malabsorption syndromes, pseudo hyponatremia in high glucose, conditions with loss of electrolytes, severe malnutrition, and unprovoked seizures were excluded.

Detailed assessments, including demographic data, complete history including nature of illness and family history, clinical examinations and laboratory investigations were done. In the present study, recurrence was defined as a seizure occurring within 24 hours during the same febrile illness. Low sodium level (Hyponatremia) was defined as serum sodium less than 134mmol/l, and normal serum sodium levels were taken as 134-144mmol/l.

Data were analyzed using SPSS software version 23.0 (IBM, USA). Continuous data were expressed as mean and Standard Deviation (SD) and compared between children with simple febrile seizure and children with complex febrile seizure by independent sample t-test. Categorical data were expressed in frequency and percentage and compared between groups using the Chi-square test. The Receiver Operating Characteristic (ROC) curve for predicting complex febrile seizures based on serum sodium levels was plotted, and the optimal cutoff value was estimated based on the Youden index. p value <0.05 was considered as statistical significance.

Results

A total of 60 children were enrolled in the study in which 36 were diagnosed with simple febrile seizures and 24 of them with complex febrile seizures. The mean age was 22.3 months and there was male preponderance with a male to female ratio of 2.3:1. The mean serum sodium level was 136.9 ± 6.5 mmol/l and 18 (30%) patients had hyponatremia.

Table I Characteristics of the patients (n=60)

Characteristics	Frequency	Percentage (%)
Age, months, mean±SD		22.3±10.0
≤24 months	38	63.3
>24 months	22	36.7
Sex		
Male	42	70.0
Female	18	30.0
Family history of febrile seizure	11	18.3
Family history of epilepsy	4	6.7
History of previous febrile seizure	20	33.3
Temperature, °F, mean±SD		102.4±1.0
Seizure type		
Simple febrile seizure	36	60.0
Complex febrile seizure	24	40.0
Serum sodium level, mmol/l, mean±SD		136.9±6.5
Hyponatremia	18	30.0
Normonatremia	37	61.7
Hypernatremia	5	8.3

Data were expressed as frequency and percentage if not mentioned otherwise.

The most frequent infection was pneumonia, diagnosed in 18 (30%) of the children, followed by URTI (28.3%) acute gastroenteritis (11.7%) (Figure 1).

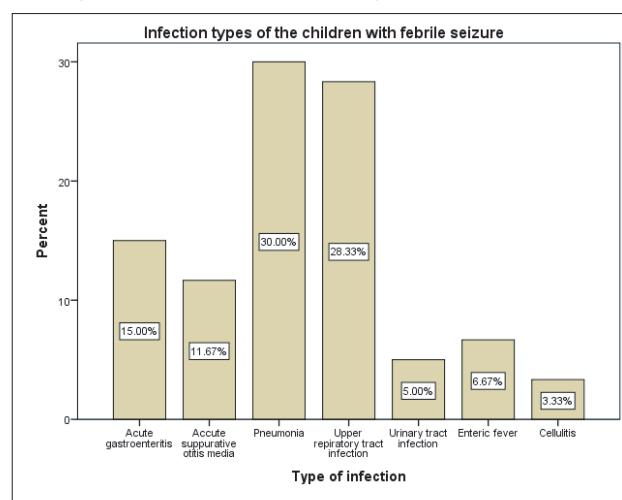


Figure 1 Distribution of the children with febrile seizure according to their infection types

Table II shows that, the mean age was lower in patients with complex febrile seizure than the patients with simple febrile seizure without any statistical significance. Similarly, though higher proportion of children with complex seizure had FH of febrile seizure and FH of epilepsy than the children with simple seizure, the differences were not significant statistically. On the other hand, the mean serum sodium levels were significantly lower in children with complex febrile seizure (134.0 ± 6.1 and 138.9 ± 6.0 , $p = 0.003$) and proportion of children with hyponatremia were significantly higher among children with complex febrile seizure than the children with simple seizure (50% versus 16.7%, $p = 0.006$).

Table II Association between different clinical features and seizure types

Characteristics	Febrile seizure type		p value
	Simple seizure (n=36)	Complex seizure (n=24)	
Age, months	23.1 \pm 10.2	21.1 \pm 9.9	0.441 [†]
Sex			
Male	22 (61.1)	20 (83.3)	0.66*
Female	14 (38.9)	4 (16.7)	
FH of febrile seizure	4 (11.1)	7 (29.2)	0.077*
FH of epilepsy	2 (5.6)	2 (8.3)	0.673*
Previous febrile seizure	14 (38.9)	6 (25.0)	0.264*
Temperature, °F, mean \pm SD	102.5 \pm 1.0	102.3 \pm 1.0	0.538 [†]
Serum sodium level, mmol/l	138.9 \pm 6.0	134.0 \pm 6.1	0.003 [†]
Serum sodium status			
Hyponatremia	6 (16.7)	12 (50.0)	0.006*
Normal or hypernatremia	30 (83.3)	12 (50.0)	

FH: Family History [†]Independent sample t test, *Chi-square test.

As shown in Figure 2, the optimal cutoff value of serum sodium level was 134.0 mmol/L with an area under the receiver operating characteristic curve (AUC) of 0.72 (95% CI: 0.59-0.86) for complex febrile seizure, with a sensitivity of 80.0% and specificity of 50.0%. The performance of the classifier was

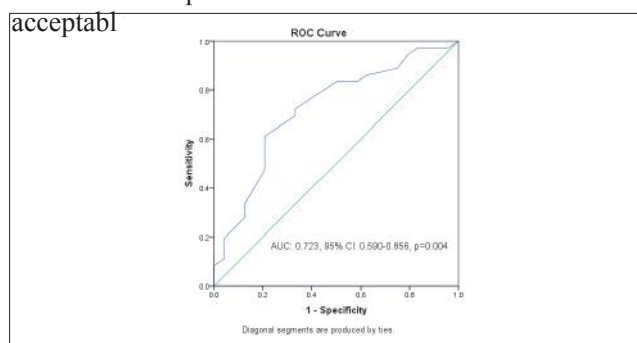


Figure 2 Receiver operating characteristic curve for prediction of complex febrile seizures based on serum sodium levels

Discussion

In the present study 60 children with febrile seizures between the age group of 6 months to 60 months were assessed, of which 63.3% children had febrile seizures between the age group of 6 months to 24 months with a mean age of 22.3 months, which agreed with results of other studies.^{17,18} The present study showed that febrile seizure was more in boys and in the previous studies the males outnumbered the females too.¹⁶⁻²⁰

The study had observed significant differences in the serum sodium levels among children with simple and complex febrile seizures. Thus, the study had confirmed the hypothesis that serum sodium levels are a predictor of complex febrile seizure. This result supports a finding of a recent meta-analysis that evaluated the serum sodium levels in febrile seizures of children with or without recurrent febrile seizure during the same episode. Their analysis suggested that serum sodium level was lower in patients with recurrent febrile seizure during the same febrile episode than in those with single febrile seizure.¹⁵ However, the present study results were contradictory to other studies that negate the relationship between lower serum sodium levels and an increased risk of developing recurrent seizures within the same febrile illness.¹⁶⁻²⁰

Studies have identified several underlying factors for febrile seizure in healthy children, including a history of antenatal complications, zinc deficiency, iron deficiency anemia, hypomagnesemia and lower body temperature (Cutoff value 39.2) as a risk factor for recurrent febrile seizure with the same episode.²¹⁻²⁵ In this study, the AUC was 0.81, which suggests that hyponatremia (Sodium level < 134.0 mmol/L) may be a more useful marker for predicting complex febrile seizure, with a sensitivity of 80% and specificity of 50%. The present study results agreed to the study of Miyagi et al. where the cutoff value of serum sodium 134.72 mmol/L had a sensitivity of 80% and specificity of 70% for prediction of recurrent febrile seizures with the same febrile episode. However, receiver-operating characteristics analysis for hyponatremia in the study of Alp et al. showed lower sensitivity (50.3%) and specificity (43.1%) values for optimal cutoff value of 133.5 mmol/L of serum sodium level.¹⁴

Limitation

The limitations of our analysis need to be addressed. First, the sample size was small. Second, there was no control group of febrile children without seizure. Finally, due to the cross-sectional design, it is not possible to conclude from this study whether complex febrile seizure is affecting hyponatremia or hyponatremia is affecting complex febrile seizure

Conclusion

In conclusion, the study showed a statistically significant relation between low serum sodium levels and complex febrile seizures. Otherwise, the possibility of predicting complex febrile seizure using sodium level < 134.0 mmol/L emerged. Hence there is a need to evaluate serum sodium levels in patients with febrile seizures.

Recommendation

There is a need for prospective studies with more extensive case series to confirm the results.

Disclosure

Both the authors declared no competing interest.

References

1. Commission on Epidemiology and Prognosis, & International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. *Epilepsia*. 1993; 34(4):592–596.
2. Sawires R, Buttery J, Fahey M. A Review of Febrile Seizures: Recent Advances in Understanding of Febrile Seizure Pathophysiology and Commonly Implicated Viral Triggers. *Frontiers in Pediatrics*. 2021;9:801321.
3. Durkin MS, Davidson LL, Hasan ZM, Hasan Z, Hauser WA, Khan N, Paul TJ, Shrout PE, Thorburn MJ, Zaman S. Estimates of the prevalence of childhood seizure disorders in communities where professional resources are scarce: Results from Bangladesh, Jamaica and Pakistan. *Paediatric and perinatal epidemiology*. 1992 Apr;6(2):166-180.
4. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures, American Academy of Pediatrics. Febrile seizures: Clinical practice guidelines for the long-term management of the child with simple febrile seizures. *Pediatrics*. 2008;121:1281–1286.
5. Patel AD, Vidaurre J. Complex febrile seizures: a practical guide to evaluation and treatment. *Journal of child neurology*. 2013;28(6):762-767.
6. Kiviranta T, Airaksinen EM. Low sodium levels in serum are associated with subsequent febrile seizures. *Acta paediatrica*. 1995;84(12):1372-1374.
7. 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 Neurol*. 2009;3:31-34.
8. Nickavar A, Hasanpour H, Sotoudeh K. Validity of serum sodium and calcium screening in children with febrile convulsion. *Acta Medica Iranica*. 2009;47:229–231.
9. Halawa I, Andersson T, Tomsom T. Hyponatremia and risk of seizures: A retrospective cross-sectional study. *Epilepsia*. 2011;52:410–413.
10. Rahman ML, Hossain B, Uddin B, Mia SH. Serum sodium level on the recurrence of febrile seizure within the same febrile illness-experience in a district level hospital. *TAJ J Teach Assoc*. 2019;32:39-45.
11. Nadkarni J, Binaykiya I, Sharma U, Dwivedi R. Role of serum sodium levels in prediction of seizure recurrence within the same febrile illness. *Neurol Asia*. 2011;16:195-197.
12. Duangpetsang J. Serum sodium levels predict the recurrence of febrile seizure within 24 hours. *J Health Sci Med Res*. 2019;37:277-280.
13. Alp EK, Elmac AM. The association between serum sodium levels and febrile seizures recurrence: is the degree of hyponatremia a risk factor?. *J Pediatr Neurol*. 2022;20:024-027.
14. Alp EK, Elmac AM. The Association between Serum Sodium Levels and Febrile Seizures Recurrence: Is the Degree of Hyponatremia a Risk Factor?. *Journal of Pediatric Neurology*. 2022;20(01):024-027.
15. Miyagi Y, Sasano T, Kato H, Kin K. Hyponatremia and Recurrent Febrile Seizures During Febrile Episodes: A Meta-Analysis. *Cureus*. 2020;14(4).
16. Benny S. Role of serum sodium levels in recurrence and recurrent episodes of febrile seizure. *Int J Contemp Pediatr* 2020;7:1606-1613.
17. Thoman JE, Duffner PK, Shucard JL. Do serum sodium levels predict febrile seizure recurrence within 24 hours?. *Pediatr Neurol*. 2004;31:342-344.
18. Maksikharin A, Prommalikit O. Serum sodium levels do not predict recurrence of febrile seizures within 24 hours. *Paediatr Int Child Health*. 2015; 35:44-46.
19. Navaeifar MR, Abbaskhanian A, Farmanbarborji A. Relation between febrile seizure recurrence and hyponatremia in children: A single-center trial. *J Pediatr Neurosci*. 2020;15:5-8.
20. Fallah R, Islami Z. Evaluation of serum sodium levels in simple, multiple and recurrent febrile convulsions. *Acta Med Iran*. 2009;47:225-227.
21. Sharawat IK, Singh J, Dawman L, Singh A. Evaluation of risk factors associated with first episode febrile seizure. *J Clin Diagn Res*. 2016;10:SC10-SC13.
22. Heydarian F, Nakhaei AA, Majd HM, Bakhtiari E. Zinc deficiency and febrile seizure: a systematic review and meta-analysis. *Turk J Pediatr*. 2020;62:347-358.

23. Kwak BO, Kim K, Kim SN, Lee R. Relationship between iron deficiency anemia and febrile seizures in children: A systematic review and meta-analysis. *Seizure*. 201;52:27-34.

24. Baek SJ, Byeon JH, Eun SH, Eun BL, Kim GH. Risk of low serum levels of ionized magnesium in children with febrile seizure. *BMC Pediatr*. 2018;18:297.

25. Kubota J, Higurashi N, Hirano D, Okabe S, Yamauchi K, Kimura R, et al. Body temperature predicts recurrent febrile seizures in the same febrile illness. *Brain and Development*. 2021;43(7):768-774.