Original Research Article

Role of serum sodium levels in recurrence and recurrent episodes of febrile seizure

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ABSTRACT

Background: Simple febrile seizures are the common childhood seizures, usually affecting 1 in 20 children between the age group of 6 months to 60 months. Earlier studies have shown an association between low serum sodium as a cause for febrile seizures and its recurrences. The present study was to determine the role of serum sodium in predicting febrile seizure recurrence within 24 hrs and recurrent episodes.

Methods: Children aged between 6 months to 60 months with first episode of febrile seizures, admitted to the Paediatric ward of MOSC medical college Kolenchery, were recruited in the study. Inclusion criteria were demographic data, family history, clinical examinations, and laboratory investigations (serum sodium and hemoglobin).

Results: Of the total study population of 100 children 33 had recurrences in 24 hours and 16 had recurrent episodes. About 57 children had a family history of febrile seizures, out which 28 children had recurrence of febrile seizure within 24 hours. 26 children had family history of epilepsy, of which only 8 had recurrences in 24 hours and 5 had recurrent episodes. Serum sodium levels of 69 children was above 130 mmol/l and 31 children had sodium level below 130mmol/l. Of 31 children, with low serum sodium levels (<130mmol/l), 29 had recurrence within 24 hours, which was not statistically significant. The sodium levels of 16 children who had recurrent episodes of seizure, was also between 130.1-135mmol/l. No significant differences were seen between the serum sodium levels in simple febrile seizures and recurrent episodes.

Conclusions: Study showed low serum sodium is not statistically significant to predict a recurrence within 24 hours, but a relative hyponatremia can predispose, a febrile child to occurrence of simple febrile seizure.

Keywords: Febrile seizure, Hyponatremia

INTRODUCTION

A Febrile seizure is a seizure accompanied by fever (temperature 100.4°F or 38°C by any method), between age of 6 months to 60 months, without CNS infection or metabolic imbalance, and that occurs in the absence of a history of prior afebrile seizures.1

Risk of recurrences in febrile convulsion is 30-40%, after first episode, 50% after 2nd or more episodes, 50% in infants <1year old.

Simple febrile seizure

A short generalized seizure, of a duration of <15min, not recurring within 24h, occurring during a febrile episode not caused by an acute disease of the nervous system, in a child aged 6 months to 5 years.

With no neurologic deficits (i.e., with no pre, peri, or postnatal brain damage), with normal psychomotor development, and with no previous afebrile seizures.1,2
**Complex febrile seizure**

A focal, or generalized and prolonged seizure, of a duration of greater than 15 min, recurring more than once in 24h, and/or associated with postictal neurologic abnormalities, more frequently a postictal palsy (Todd’s palsy), or with previous neurologic deficits.3

**Febrile status epilepticus**

Is a febrile seizure lasting more than 30 mts, or by shorter serial seizures, without regaining consciousness in the interictal state.3,4

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<thead>
<tr>
<th>Major</th>
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<tr>
<td>Age &lt;1year</td>
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**Pathophysiology**

Febrile Seizure are the most common paroxysmal episode during infancy and childhood, which affects up to one in 10 children. These seizures are associated with high grade fever in children and is a major cause of emergency visits and a source of family anxiety.5

Febrile seizure is a benign condition, where the etiology or pathophysiology is not yet clear, however emerging febrile seizure syndromes behave differently.

Genetic predisposition is thought to be a major contributor. A strong family history of febrile convulsions in siblings and parents suggests a strong precipitating factor. Genetic studies show a multi factorial mode of inheritance. Siblings with history of Febrile Seizure showed 10-20% of recurrences.5 An autosomal dominant inheritance pattern, where found in genes encoding the sodium channel and the gamma amino- butyric acid receptor A.7 Percentage of recurrence, if one of the parents had history of Febrile Seizure chance of recurrence is about 40%. In case of twins, about 70% had shown risk of developing Febrile Seizure.5,6

Certain channelopathies like mutations in sodium channel receptor and gamma-aminobutyric acid (GABA) receptor genes, has shown association with febrile seizures. There are a number of known linkages for febrile seizures. FEB1 and FEB2 have been suggested on chromosome 8 and 19p respectively and involve only FS.

Viral infections or fever (viruses), have postulated that it produces, an abnormal immune response to an infection and elevated cytokine levels, which can increase the seizure threshold and results in febrile seizure. Cytokines like IL-1 beta have reported to be associated with pathogenesis of FS. Double stranded RNA is a common viral component, which induces host cell immune responses. A significant levels of IL-1 beta from double stranded RNA - stimulated leukocytes is reported to cause FS. Earlier studies have shown that both astrocytes and microglia secrete numerous cytokines like IL - 1 beta, TNF-a, IL-6 which will take part in inflammation and infection.6

A low threshold of developing cerebral cortex, has more susceptibility of a child to infections and the propensity to develop high grade fever and genetic component are the other factors which causes convulsive threshold. A low threshold, probably initiated from a combination between increased excitation and reduced inhibition, in addition to other maturational differences in subcortical circuits.8

Vaccines and febrile seizures have a strong association, both febrile and afebrile seizures can happen after immunization.6,7

A significant association was found between Iron deficiency anemia and febrile seizures. It can also be a risk factor.10 A study of febrile seizure in Indian children has shown that lower zinc levels can also be a risk factor.11

Epilepsies associated with febrile seizure includes generalized epilepsy with febrile seizure plus (GEFS+), absence epilepsy, hippocampal sclerosis and non-febrile partial seizures following FS.12 Ohtahara syndrome, FIRES, Dravet Syndrome. But mechanism of seizure is different in each.

Fever can also cause disturbances in fluid and electrolyte balances; hyponatremia is found as a predisposing factor for recurrence of another seizure.

As sodium plays an important role in cell physiology, neuronal cell depolarisation, production of electrical discharges and finally seizures, the need to evaluate and
Hyponatremia

It is defined as serum sodium level <135mEq/L. It is classified based on patient’s volume status.

Correlate serum sodium levels in febrile seizures become significant. Various literatures showed that sodium plays an important role in cell physiology and neuronal stimulation in developing seizures. Sodium is an important electrolyte needed for the function of all the cells in the body. Nerve cells are particularly sensitive to the amount of sodium in the blood because they need electrolytes to function properly. Too much or too less of sodium can cause problems with the nerves in this brain or elsewhere in this body.

In 1993, Lennox suggested the importance of hydration and increased permeability of cell membranes as a mechanism of febrile seizures. Elevation of the “threshold” to febrile seizures occurs with increasing age, which is associated with developmental changes in the balance of water and electrolytes, especially hyponatremia.

Sodium metabolism: body content and physiologic function

Sodium is the dominant ion in the extra cellular space and is extremely important in the maintenance of osmotic gradients and electrical neutrality in the body. It is necessary for the maintenance of intravascular volume. Less than 3% of sodium is intracellular. 40% of total body sodium is present in the bone and the remaining is in the interstitial and intravascular spaces.

Intake: Child’s diet determines the amount of sodium ingested. Infants receive sodium from breast milk (~7mEq/L) and formula (7-13mEq/L, for 20calorie/oz formula). Sodium is readily absorbed in the gastrointestinal tract. Glucose enhances sodium absorption owing to presence of a cotransport system, which is the rationale for including sodium and glucose in oral rehydration solution.

Excretion: Sodium excretion occurs mainly through stool and sweat, the kidney regulates sodium balance and it is the principal site of sodium excretion. Sweat has 5-40mEq/L of sodium. Sweat sodium concentration will be increased in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism, which can contribute to sodium depletion. Less than 2% is found in feces, but in diarrhea large quantities are lost in faeces.

The main biochemical functions of sodium include, it regulates acid - base balance, maintenance of osmotic pressure and fluid balance, normal muscle irritability and cell permeability, absorption of glucose, galactose and amino acids and for initiating and maintaining heart rate.

Hypovolemic hyponatremia

Here the child loses sodium from the body, the water balance may be positive or negative, but sodium loss is higher than water loss. Most fluid lost from the body has lower sodium concentration. Hyponatremia exists when the ratio of water to sodium is increased.

Pseudohyponatremia is a laboratory artifact which present as, the plasma contains very high concentrations of protein (multiple myeloma, intravenous immunoglobulin infusion) or lipid (hypertriglyceridemia, hypercholesterolemia). Hyperosmolality, may occur with hyperglycemia, with a low serum sodium concentration as water moves down its osmotic gradient from the intracellular space into the extracellular space, hence dilution of the sodium concentration occurs. However, patients with hyponatremia resulting from hyperosmolality do not have symptoms of hyponatremia.

Classification of hyponatremia is based on the patient’s volume status. In hypovolemic hyponatremia, the child has lost sodium from the body. The water balance may be positive or negative, but sodium loss is higher than water loss. Hyponatremic state can be isotonic, hypertonic, hypotonic according to sodium concentration.

The pathogenesis of the hyponatremia is a combination of sodium loss and water retention to compensate for the volume depletion.

Hyponatremic encephalopathy can be a combination of brain swelling and increased intracranial pressure, which can lead to increased pressure in the brain, decreased cerebral blood flow, resulting in cerebral herniation. Hyponatremia can develop in infants less than 6 months of age, when caregivers offer water to their infant as a supplement, during hot weather, or when they run out of formula, which can result in transient seizures. If the infant appears thirsty, the parent should offer formula or breastfeed the child.

Various studies and literatures have shown association between hyponatremia and febrile seizures. Sakha K, Barzgar M, stated that in exposure groups the mean sodium levels was 135.4±4 meq/L lower than control groups (137.94±2.92). There was statistically significant difference between two groups (p<0.001).

A study done by Kiviranta T, Airaksinen EM, showed that sodium concentrations were lowest in children with repeated seizures and that hyponatraemia may increase the for multiple convulsions during the same febrile illness.

Chiarelli F stated that in patients with febrile convulsions serum levels of sodium, calcium and osmolarity were significantly lower than those obtained in both control groups.
Sayedzadeh S.A, Hemati M. confirmed that serum sodium and calcium level in patients with febrile convulsion is not a predictor factor for recurrence of seizure.22 Fallah R, Islami Zia stated that there was no significant difference in age and serum sodium level among the case and control groups. Association of relative hyponatremia and febrile seizure recurrence was not confirmed. These findings reaffirm the recommendation of the American Academy of pediatrics not to routinely obtain electrolytes in febrile convulsion unless clinically indicated.23

A study done by Heydrian F and colleagues, to know the role of serum sodium levels in prediction of seizure recurrence during the first 24 hours, showed that although serum sodium levels cannot assist in prediction of recurrence of simple febrile seizures in children, relative hyponatremia may predispose the febrile child to occurrence of simple febrile seizure.24 Hugen C A, Oudesluys M, stated that measurement of serum sodium was a valuable investigation in the child with febrile seizure. Lower the serum sodium levels, the higher the probability of a repeat convulsion.4

Study done by Nadkarni J showed, that there was no significant difference in the mean serum sodium levels between children with FS (137.1 SD 4.1 mmol/L) and control (138.2SD 4.3 mmol/L). Within the febrile seizure group, the mean serum sodium level in the children with recurrent seizures was significantly lower than the mean in those with a single seizure (134.3 SD 3.8 mmol/L) versus 138.2 SD 3.7 mmol/L, p<0.01. Univariate analysis showed no difference in age, gender, temperature, history, or family history of febrile seizure between those with a single seizure and those with recurrent seizures.25

Rutter N and O’Callaghan M J, stated that hyponatremia is a common feature seen in children with febrile seizures, where majority of cases had an evidence of mild inappropriate secretion of ADH. In a study of 23 children with febrile seizures, mild hyponatremia was seen in 8 cases, in which 6 cases had evidences of inappropriate secretion of ADH.25

METHODS

This was a hospital based cross sectional study conducted M.O.S.C Medical College, Kolenchery, Department of Pediatrics for the duration of one year from May 2015-May 2016.

The sample size was calculated based on a study done by Jayasheer Nadkarni which noted that 27% of children with febrile seizures had a sodium less than 135.24 This sample was calculated for a single proportion using n master sample size calculator computer software using the formula n=Z21-α/2P(1-P)/d2.26 The sample size was found to be 76 for an absolute precision of 10% for a confidence interval of 95%. Study population includes all children with febrile seizures aged between 6 months - 60months, who gets admitted at the department of Pediatrics of MOSC medical college, Kolenchery for a period of one year.

Inclusion criteria

- Children with first febrile seizures.
- Age group between 6 months - 60 months.

Exclusion criteria

- Neurodevelopmental delay.
- Meningitis, encephalitis.
- Malabsorption syndromes.
- Pseudohyponatremia in high glucose.
- Conditions with loss of electrolytes, SIADH.
- Severe malnutrition.
- Unprovoked seizures.
- Children using drugs like diuretics.

Study tools was data collection proforma

Data collection process

Informed consent was obtained from all children who presented with first episode of febrile seizure aged between 6 months to 60 months who were admitted in MOSC medical college Detailed assessment including demographic data, complete history included nature of illness and family history, clinical examinations and laboratory investigations were done.

In the present study

- Recurrence is defined as seizure occurring within 24 hrs during same febrile illness.
- Recurrent episode is defined as a seizure occurring any time after first episode with fever or after 24 hrs. of fever.
- Low sodium level (hyponatremia) is defined as serum sodium less than 130meq/l.
- In this laboratory the normal serum sodium levels in children is taken to be 130-145meq/l.
- Thus, sodium serum levels are divided into ≤130,130.1-135,135.1-140,140.1-145,>145

Data analysis

The study was analyzed with SPSS software version 24. For all the tests, p value of <0.05 was considered as statistically significant.

RESULTS

Among the 100 children with first episode of febrile seizures, 68% children with febrile seizures were between
the age group of 6 months to 24 months, peaking at 15-19 months, 22% were between 24 months to 42 months and 10% between 42 months to 60 months.

(p<0.05) (Figure 4). Among all children, 33% had sodium level between 130.1-135mmol/l, 31% had sodium levels between ≤130mmol/l and 36% had sodium levels >135mmol/l (Figure 5).

Among the 100 children, 57% were males and 43% were females. Male to female ratio was 1.3:1. Male gender predominance was noted in this study.

In this study conducted, 62% children had temperature between 100°F-101°F, at the time of presentation. No statistical significance was noted between temperature at the time of presentation and recurrence of febrile seizure.

Out of 100 children, 57 children had family history of febrile seizures, of which 28 children had recurrences within 24 hours, which was found statistically significant (p<0.05). Among all children, 33% had sodium level between 130.1-135mmol/l, 31% had sodium levels between ≤130mmol/l and 36% had sodium levels >135mmol/l (Figure 5).

Among the 31% children with low serum sodium levels <130 mmol/l, 29 had seizure recurrence within 24 hours. Rest 69% children sodium levels were >130mmol/l of which 4 had seizure recurrence. This was not statistically significant (p>0.05). Hence serum sodium levels in
patients with febrile seizure was not a predictor factor for seizure recurrence (Figure 6).

Hemoglobin values were measured in 100 children, of which 66% children had hemoglobin values ranging between 7-11gm%, 33% had hemoglobin between 11-14gm% and 1% had hemoglobin <7gm%.

**Figure 7: Distribution of hemoglobin levels.**

Among 100 children, 38% had upper respiratory tract infection, 32% had viral fever and 30% had other causes (ASOM 6, herpangina 17, Urinary tract infection 6, a/c tonsillitis 2).

**Figure 8: Distribution: causes of fever.**

**DISCUSSION**

In the present study 100 children with first febrile seizures between the age group of 6 months to 60 months where assessed, of which 68% children had febrile seizures between the age group of 6 months to 24 months peaking at 15 - 19 months, which was in agreement with results of other studies. A study done by Al Eissa, found mean age of presentation was 15 months. Male to female ratio was 57:43 (1.3:1). Male gender predominance was almost well documented in previous studies. In this study 62% children had temperature between 100°F-101°F, at the time of presentation, a study done by El Radhi found that children with lower temperature has highest chance of recurrence than higher temperatures. But in this study only 23 had recurrence, which was not statistically significant. From 100 children 33 had recurrences within 24 hours and 16 had recurrent episodes. About 57 children had family history of febrile seizures, out which 28 children had recurrences within 24 hours. 26 children had family history of epilepsy, from which only 8 had recurrences in 24 hours and 5 had recurrent episodes. Family history of febrile seizures was found as a significant risk factor for febrile seizures, which was found to be in agreement with studies done by Essam J Al Zwaini and colleagues where 33% had family h/o febrile seizure. Another study by Doose H, showed a multifactorial polygenic mode of inheritance and off springs with maternal history of febrile seizure had shown increased risk. Genetic origin of febrile seizure with autosomal dominant inheritance is also seen.

Degree of fever, gender, family history of febrile seizures was not found as risk factors in the study done by Al-Eissa. Regarding the causes of fever 38% had upper respiratory infection, 32% had viral fever and 30% had other causes (ASOM 6, herpangina 17, UTI 6, a/c tonsillitis 2). From this study upper respiratory infection was not a significant predisposing factor for febrile seizure. The finding was similar with study done by Essam J, but it differs from a study done by Tang J to know the relationship between upper respiratory infections and febrile seizures in china showed. From 100 children with febrile seizure, the serum sodium levels of 69 was above 130 mmol/l and 31 had below 130mmol/l. Of 31, with low serum sodium levels (<130mmol/l), 29 had seizure recurrence within 24 hours, which was not statistically significant. Sayedzadeh, S.A Hemati, M. also stated the study re-confirmed that serum sodium level in patients with febrile convulsion is not a predictor factor for recurrence of seizure. F Heydrian, in his study also stated that although serum sodium levels cannot assist in prediction of recurrence of simple febrile seizure in children, relative hyponatraemia may predispose the febrile child to occurrence of simple febrile seizure. This study was in contrary to the study done by Hugen C A, also found that measurement of serum sodium was a valuable investigation in the child with febrile seizure. Lower the serum sodium levels, the higher the probability of a repeat convulsion. Kiviranta T and Airaksinen E M showed that sodium concentrations were lowest in children with repeated seizures and that hyponatraemia may increase the risk for multiple convulsions during the same febrile illness. Majority of the children in this study had serum sodium levels between 130.1-135 mmol/l. The sodium levels of sixteen children who had recurrent episodes of seizure, was also between 130.1-135mmol/l. No significant differences were seen between the serum sodium levels in simple febrile seizures and recurrent episodes. Hemoglobin was measured in 100 children, in which 66 percent were found to be anemic, (HB levels range between 7-11gm%). This agreed with
many studies done by various authors. A case control study done by Leela Kumari found iron deficiency anemia as a significant risk factor for simple febrile seizures.10 The calcium and sugar levels of the children in this study was within normal limits, similar with study done by N Rutter and O R Smales. The main limitation of this study was being a hospital-based study and it did not have an additional group which included febrile patients without seizures. This study showed no statistically significant relation between serum sodium levels in recurrence and recurrent episodes of febrile seizures. Hence there is no need to evaluate serum sodium levels in patients with simple febrile seizures. Authors suggest conducting an extensive study to know a correlation between serum sodium levels and febrile seizures.

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26. Sample size measured using Master sample size calculation software produced by Master of biostatistics, Christian medical college, Vellore 632 004, Tamil Nadu, India.

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