

Profile of Febrile Seizures in Children and Association with Serum Sodium Levels in a Tertiary Centre in Sokoto, Nigeria

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ABSTRACT

Background: Febrile seizures (FS) are a major presentation of young children with febrile illnesses. They may occur recurrently within the same febrile illness. This study sought to examine the profile of children with febrile convulsions and association of hyponatremia with recurrent febrile seizures. **Methodology:** The study determined the clinical characteristics, recurrence pattern and serum sodium level of children with FS admitted into the Department of Paediatrics of Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto, Nigeria. It was a retrospective study from January 2019 to December 2020. Cases were children aged 3 months to 6 years admitted with FS. Their case folders were extracted and relevant data entered into a proforma sheet and data was analyzed using SPSS version 23. **Results:** 357 of 4583 (7.8%) admitted children had FS, 230 were male (64.4%) with M:F ratio of 1.8:1. Their age ranged from 3 to 72 months with mean of 33.6 (± 17.3) months. 201 (56.3%) had simple FS while 156 (43.7%) had complex FS. Higher proportion of females had complex FS though not significant ($\chi^2=0.61$; $p=0.73$). The commonest documented cause of fever was malaria (70.3%). 177 (49.6%) had recurrent episodes FS on admission. Of the total, 118 had serum sodium results retrieved, 60 (50.8%) had hyponatremia with mean level of 129.3mmol/l (± 5.5); this was slightly lower in those with recurrent seizures within the illness but not significant. It was also lower in those with complex seizures especially those with higher temperature on admission. There were 6 mortalities and these included cases initially diagnosed with complex FS but later developed febrile status epilepticus and died. **Conclusion:** Febrile seizures are a significant presentation in children. About half had associated hyponatremia which was associated with recurrent seizures though not significant. Those with complex FS had hyponatremia which was more significant with fever at presentation. Mortality occurred in those that had febrile encephalopathy.

Keywords: Febrile seizures, Children, Recurrence, Hyponatremia, Serum, Sodium.



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INTRODUCTION

Febrile seizures (FS) in childhood is a common but benign neurological disorder characterized by convulsions associated with fever due to the effect of fever on the immature brain.^[1] A febrile seizure is defined by the International League Against Epilepsy (ILAE) as a seizure occurring in childhood after one month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures.^[2] Febrile seizures are most common between the ages of 6 months and 6 years and have a peak incidence at 18 months.^[3] They usually occur at temperature more than 38°C or 100.4 F in the absence of intracranial infections or other metabolic disturbances.^[4,5] They may also occur at temperatures of less than 38°C (37.6°C to 37.9°C) and lower temperature is a risk factor for recurrence of febrile seizures after an initial episode.^[1] The mechanisms underlying FS have multifactorial causes and the pathogenesis of FS is unknown however most of the proposed mechanisms represent a point between a low seizure threshold and genetic predisposition.^[6] The conditions which should be excluded include central nervous system infections, metabolic derangements of glucose (hypoglycemia), sodium (hypo or hypernatremia), calcium (hypocalcemia), magnesium (hypomagnesemia), head trauma and drug withdrawal. There should also not be any past history of neonatal seizures, a previous unprovoked seizure or they must not meet criteria for other acute symptomatic seizures.^[1,7]

Figures from the United States and United Kingdom show that the prevalence averages 2%-5% of children under five years while higher figures are reported from the Asian continent and also Africa.^[8] It is more commonly seen in Asian communities (5-10% of Indian and 6-9% of Japanese children).^[9,10] There are two types: simple and complex febrile seizures. A simple FS is single, brief, generalized and lasts less than 15 minutes.

Complex FS on the other hand, have a focal onset, occurs more than once in 24 hours during a febrile illness, and lasts more than 15 minutes. Febrile status epilepticus (FSE) is a subgroup of complex FS which is defined as a febrile seizure lasting 30 minutes or more.^[11] Most FS are simple with approximately 20-30% being complex.^[8]

Febrile seizures in children may be distressing to family members and care givers. The attending physician must be able to appropriately manage the situation, exclude causes of CNS infection, put measures to prevent prolonged FS and also assess for risks of recurrence even within the same febrile illness so as to appropriately counsel the family.

The pathogenesis of FS has been linked to many factors including a low threshold in susceptible children from a combination between increased excitation and reduced inhibition, an abnormal immune response to an infection and elevated cytokine levels which can increase the seizure threshold and results in febrile seizure, genetic predisposition as strong family history of febrile convulsions in siblings and parents exists, hyponatremia has also been found to be a predisposing factor for recurrence of another seizure.^[12,13]

Sodium plays an important role in cell physiology, neuronal cell depolarization, production of electrical discharges and finally seizures. Sodium is the major cation of extracellular fluid and is associated with cell membrane function, formation and transmission of action potentials in acetyl cholinergic synaptic transmission.^[6,14] Studies have indicated that measurement of serum sodium amongst other parameters in children may help assess the possibility of recurrence within same illness.^[15-19]

This study was carried out to assess the pattern of presentation of FS and relationship of seizures occurrence to serum sodium levels. Such study has not been done in the Nigerian setting.

METHODOLOGY

Study area

The study was carried out at the Emergency Paediatric Unit Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto, Nigeria., a tertiary health facility located in the Sokoto State capital. It has an annual average temperature of 28.3°C, with the highest temperatures reaching up to 45°C during the hot dry months. The rainy season is short and begins late in May till September with a mean annual rainfall of 550mm. The dry season comprises the hot dry season before the rains from March to April and the cold dry season from November to February.^[20] There is intense malaria transmission throughout the year with peaks during the rainy season.^[21] Also, some viral infections causing acute respiratory infection are also transmitted highly during the wet season and others like measles and rotavirus during the dry season.^[21, 22]

Study design

This was a retrospective study conducted over a 2-year period (1st January 2019 to 31st December 2020)

Study subjects

Comprised children aged 1 month to 6 years admitted into the EPU with acute febrile illness and associated convulsions who were eventually managed till discharge as cases of febrile seizures. Their diagnosis was based on ILAE criteria of simple FS and complex FS.^[8]

Inclusion criteria

1. Any child who is aged 1 months to 6 years and admitted with fever (axillary temperature > 37.5°C) and convulsions diagnosed to be febrile convulsions at point of admission

Exclusion criteria

1. Any child with past history of afebrile seizures
2. Any child with features of neurological syndrome

3. Any child whose diagnosis was changed during the course of admission to include CNS pathologies like measles with encephalitis, meningitis, and cerebral malaria were excluded.
4. Those with severe malnutrition, anaemia and diarrhoea were also excluded

Procedure of patient recruitment

All children with fever (axillary temperature >37.5 °C) and convulsions were enrolled to the study. Simple FS was diagnosed if the seizure was single within 24 hours, generalized and lasted less than 15 minutes. Complex FS was diagnosed if the seizure was focal in onset, occurred more than once in 24 hours or lasted more than 15 minutes. Those who had simple FS or complex FS and had repeat convulsions with fever after admission and commencement of treatment were also noted.

Those whose diagnosis were changed along the way to include CNS pathologies were excluded like meningitis, cerebral malaria and measles with encephalitis (this was differentiated from measles with febrile convulsions where the child regained consciousness immediately). Those with severe malnutrition, anaemia and diarrhoeal disease were also excluded due to the possible influence on the serum sodium level.

Data entry and analysis

The demographic, clinical characteristics including age, gender, type of febrile convulsion, precipitating infection, past history and family history. Repeat episodes of convulsion during the admission, serum sodium and full blood count were also documented.

RESULTS

Socio-demographic characteristics of patients

There were 357 children admitted for FS out of 4583 children admitted during the period accounting for 7.8% of the total. There were 230

males (64.4%) and 127 females (35.6%) with M:F ratio of 1.8:1. Their age ranged from 3 to 72 months with mean of 33.6 (± 17.3) months. 241 (67.5%) were aged less than 3 years.

Monthly prevalence

During the two-year period of the study, the highest number of cases were seen in the month of August to December accounting for 224 (61.7%). This coincided with the rainy season peak from August to October and onset of the cold dry season from late November onward (Figure 1).

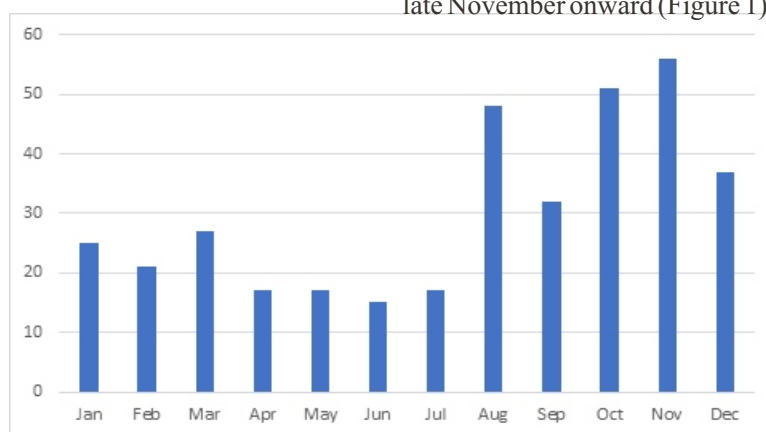


Figure 1: Monthly distribution of the admitted cases of febrile seizures

Type of Febrile seizures

Out of 357, 201 (56.3%) had simple FS while 156 (43.7%) had complex FS. There was no significant relationship between the type of FS and gender ($\chi^2=0.61$, $p = 0.43$) however, higher proportion of the females had complex seizures as shown in

Table 1: Gender distribution of the children with Febrile seizures (n = 357)

| Age (Months) | Male n (%) | Female n (%) | Total n (%) |
|--------------|-------------------|-------------------|--------------------|
| Simple FS | 133 (57.8) | 68 (53.5) | 201 (56.3) |
| Complex FS | 97 (42.2) | 59 (46.5) | 156 (43.7) |
| Total | 230 (64.4) | 127 (35.6) | 357 (100.0) |

$\chi^2=0.61$, $df=2$, $p=0.43$

Table 2: Age distribution of the children with Febrile seizures (n = 357)

| Age (Months) | Below 36 months n (%) | Above 36 months n (%) | Total n (%) |
|--------------|-----------------------|-----------------------|--------------------|
| Simple FS | 140 (58.4) | 61 (49.2) | 201 (56.3) |
| Complex FS | 101 (41.6) | 55 (50.8) | 156 (43.7) |
| Total | 241 (66.9) | 116 (33.1) | 357 (100.0) |

$\chi^2=0.96$, $df=2$, $p=0.32$

Table 1. Table 2 show that higher proportion of those with complex FS were above 3 years of age ($\chi^2=0.96$, $p = 0.32$).

Causes of FS

The commonest documented cause of fever was malaria (70.3%) followed by pharyngotonsillitis in

Table 3: Causes of fever in children with febrile seizures (n = 363)

| Diagnosis | Number | % |
|-------------------------|------------|--------------|
| Malaria | 251 | 70.3% |
| Pharyngotonsillitis | 53 | 14.8% |
| Bronchopneumonia | 23 | 6.4% |
| Urinary tract infection | 17 | 4.8% |
| Measles | 13 | 3.6% |
| Total | 357 | 100.0 |

14.8%, bronchopneumonia in 6.4%, urinary tract infection in 4.8%, 3.6% had measles. Table 3 shows the details of the diagnosis associated with FS.

Family history, past history of FS and repeat seizures on admission

116 (31.9%) had family history, 141 (39%) had past history of FS while 177 (48.7%) had repeat convulsions on admission. The proportion of those with repeat convulsions after admission was more among the males ($\chi^2=24.0$; $p=0.000$) as in Table 4.

Table 4: Repeat convulsions after admission (n = 357)

| Age (Months) | Male | Female | Total n (%) |
|--------------------|-------------------|-------------------|--------------------|
| Repeat convulsions | 136 (59.1) | 41 (32.3) | 177 (49.6) |
| None | 94 (40.9) | 86 (67.7) | 180 (50.4) |
| Total | 230 (66.9) | 127 (33.1) | 357 (100.0) |

$\chi^2=23.5$, $df=2$, $p=0.0001$

Serum sodium levels in relation to repeated seizures after admission, age type of convulsion and temperature at presentation

Of 118 who had serum sodium results available, 60 (50.8%) had hyponatremia (<135mmol/l) with mean level of 129.3mmol/l (± 5.5); this was slightly lower in those with repeated seizures within the illness but not significant [127.9 mmol/l (± 6.2) vs 129.6 mmol/l (± 4.9); $t = -8.1$; $p = 0.44$]. The value was lower amongst those above 3 years of age [130.4 mmol/l (± 6.4) vs 134.7 mmol/l (± 5.7); $t = -2.5$; $p = 0.03$],

Thirty-seven of the 118 cases of FS with serum sodium results (31.4%) presented with temperature

less than 38°C (37.6-37.9°C). Those who had temperature of $\geq 38^\circ\text{C}$ (81/118; 68.6%) at presentation had significantly lower serum sodium levels of 132.5 mmol/l (± 6.6) vs 136.4 mmol/l (± 2.8); [$t = -3.1$; $p = 0.03$] and higher total leucocyte count ($t = -2.64$; $p = 0.01$) ie 11,843 vs 8,613 cells/ul.

Also, those who had complex FS also had lower serum sodium levels compared to simple FS, though this was not significant [132.8 mmol/l (± 7.2) vs 134.4 mmol/l (± 4.5); $t = -1.1$; $p = 0.28$]. However, when only those with temperature of $\geq 38^\circ\text{C}$ at presentation were analysed ($n = 81$), the difference became significant between those with complex FS and simple FS [127.1 mmol/l (± 6.5) vs 131.4 mmol/l (± 3.2); $t = -2.3$; $p = 0.03$] (Table 5).

Table 5: Relationship between febrile seizures and serum sodium levels ($n = 118$)

| | Mean serum sodium level | Test of significance |
|--|--|--|
| Complex FS 64 (54.2%) | 132.8 mmol/l (± 7.2) | $t = -1.1$ $p = 0.28$ |
| Simple FS 54 (45.8%) | 134.4 mmol/l (± 4.5) | |
| Complex FS* 41 (50.6%) | 127.1 mmol/l (± 6.5) | $t = -2.3$ $p = 0.03$ |
| Simple FS* 40 (49.4%) | 131.4 mmol/l (± 3.2) | |
| Repeat FS 61 (51.7%) | 127.9 mmol/l (± 6.2) | |
| No repeat FS 57 (48.3%) | 129.6 mmol/l (± 4.9) | $t = -8.1$ $p = 0.44$ |
| Temperature $\geq 38^\circ\text{C}$ 81 (68.6%) | 132.5 mmol/l (± 6.6) | $t = -3.1$ $p = 0.03$ |
| Temperature 37.6-37.9°C 37 (31.4%) | 136.4 mmol/l (± 2.8) | |

* = only those with temperature $\geq 38^\circ\text{C}$ ($n = 81$)

Outcome

There were 6 mortalities comprising 5 males and 1 female. All were aged below 3 years. They did not have previous history of febrile seizures. They had repeat seizures despite multiple anticonvulsants with subsequent loss of consciousness and died within 24 hours of presentation.

Table 6: Outcome of children with febrile convulsions ($n = 363$)

| | Number | % |
|-------------------|------------|-------------|
| Discharged | 351 | 98.3% |
| Died | 6 | 1.7% |
| Total | 357 | 100% |

DISCUSSION

This review of children admitted with febrile seizures shows that it is a common presentation among admitted children accounting for 7.8% of admissions. This is slightly higher than similar report from Aba and Port Harcourt, Nigeria where 5.7% and 6.7% was reported^[23, 24] but lower than Olowu and Adeboye who reported 12% & 10% respectively from Sagamu and Ilorin. Also, Olubosede and Ibeziako from Ilesa and Enugu had much higher prevalence of 18% and 21.5%

respectively.^[25, 26] Reason adduced for studies with higher prevalence was that they were more of prospective rather than retrospective studies. The index study also retrospective of which some data can be lost.^[25] Generally these figures are higher than those of other centres in other region such as the Middle East, India and the U.S probably due to some environmental and genetic factors.^[1]

Most of the cases were due to malaria similar to other studies in the country which ranged from 52.6% and 80.4%^[23, 25, 27] though the proportional prevalence was higher in this study area possibly due to intense malaria transmission during the short rainy months. It has been reported by Nakakana et al^[21] that malaria transmission was intense during these months in Sokoto probably due to the flooding and drainage overflows which occur during the period. Supporting this, most of the cases of FS were seen in the months of September to October during the intense rains. The other main causes of febrile seizures such as pharyngotonsillitis, diarrhoea, pneumonia and measles FS occur mainly during the dry season. Other studies outside the continent showed flu as the predominant cause of FS with seasonal peaks during the flu season mainly during the cold months.^[12] A study from Italy showed a seasonal peak in January. Many studies have supported the conclusion that FS have a peak in the winter and end of the summer.^[1, 28, 29] Influenza A has been found to have a significant relationship with recurrence of FS. It has also been suggested that FS are more likely to occur with respiratory illnesses compared to viral gastrointestinal illness though any febrile illness predominant in the area may be the main cause as seen for malaria in this study area.^[1, 29]

The age range of FS captured in this study was 3 months to 6 years. Some reports indicate that they can occur as early as 3 months and may continue till the child is 6 years.^[25] Some have reported them in children up to 12 years.^[30] There were children seen with diagnosis of febrile seizures up to 9 years of age but these were excluded from this analysis. It was not clear whether they may have developed afebrile seizure disorder as a complication of

complex febrile seizures. In a more recent update, other terms such as FIRES & GEFS+ are used for this presentation of children above 6 years with seizures and fever.^[31] Generalized Epilepsy with Febrile Seizures (GEFS+) This category is a heterogeneous familial syndrome with patients displaying FS usually after the age of 6 years, in addition to having afebrile seizures too. It is thought to be inherited through an autosomal dominant mode.^[31] On the other hand, Febrile Infection Related Epilepsy Syndrome (FIRES) is an emerging disease entity closely related to FS and epilepsy which is thought to be familial or associated with mitochondrial dysfunction. Most are aged between 3 to 15 years old, and boys are affected.^[31]

The mean age in this study was 33 months similar to other reports in the country^[23-26] but higher than 15 to 18 months as reported by studies from India and China.^[7, 12] The mean age may reflect the predominant diagnosis responsible for fever. Malaria is common in the study area and peak age of affectation has been put around 2nd to 3rd year of life.^[32] More than two-thirds of the cases of FS were male, a finding which was consistent with most reports^[1, 24-26, 30, 31, 33] and the reasons adduced for this has been genetics and increased susceptibility to organisms that cause febrile illnesses like bacterial and viral infection. Case-control studies have found the male to female ratio to be 1.4:1.^[7] For the type of seizure in relation to gender, there was no relationship which is consistent with the previous reports which did not show significant difference between two genders for simple or complex seizures.^[1, 7, 8, 23, 25, 26, 33] More of the males also had a tendency to have repeat seizures after admission which was the finding in previous reports.^[1, 4, 7, 27-29, 34]

Just over half of the patients with FS had hyponatremia similar to the finding by Benny^[12] from India. This is an associated finding with febrile seizures. Relative hyponatremia is said to potentiate seizures by reducing the thresholds to seizures.^[13] This is even worse in the presence of fever which may cause fluid shifts within the brain. The mean level of those with recurrent seizures in

this study was lower but did not attain statistical significance. Some studies have shown hyponatremia increases risk for having repeat seizures within the same febrile illness.^[16, 18, 35] Rahman and Kulandaivel showed that the probability of recurrent seizures was significantly related to serum sodium level and opined that this could be used in clinical decision on the need for admission after a single FS.^[18, 35] Also, complex febrile seizures which in some instances imply more than one/ recurrent seizures in a 24-hour period in some series have been associated with hyponatremia.^[35] In this study, the mean level of sodium in those with complex FS was also lower, a finding that was more significant when those without fever at presentation were excluded. This additionally confirmed the effect of fever and sodium interaction in the recurrence of FS. Benny showed low serum sodium is not statistically significant to predict a recurrence within 24 hours, but a relative hyponatremia could predispose, a febrile child to occurrence of FS.^[12] Park on the other hand found that in a case control study, those with FS had significantly lower serum sodium than febrile controls without seizures and this also predicted recurrent seizures in them.^[17] This is similar to what Kiviranta found as sodium concentrations were lower in children with repeated seizures.^[36] Other authors like Hugen reported the probability of a repeat convulsion within the same febrile period appeared to be significantly related to the serum sodium level.^[37] Complex seizures were associated with lower serum sodium levels and this was lower in those with higher temperature at presentation in this study. Salehiomran also reported similar findings in his case control study where the mean level of serum was lower in those with complex FS compared to those with simple FS with the level being lower in those with fever at presentation.^[38] The low serum sodium also predicted recurrence of seizures in that study. Also, the finding of association of hyponatremia with the degree of temperature on admission was also reported in that study. Rashied and Alps also concluded that there

is a significant association between complex FS and lower level of serum sodium.^[15, 19] Another opinion by Sawires however does not advocate routine sodium measurement because it may not alter the management course rather if other clinical features indicate the need for these investigations, such as prolonged post-ictal drowsiness or suspicion of bacteraemia.^[33] All the mortalities associated with FS presented initially as complex FS. These patients all had prolonged seizures known as febrile status epilepticus (FSE) and died within 36 hours of admission. They were managed as cases of febrile encephalopathy. Another possibility is that they developed raised ICP from cerebral oedema as a result of the prolonged seizures or syndrome of inappropriate antidiuretic hormone secretion (SIADH) which is associated with hyponatremia. Febrile seizures are usually not associated with notable mortality however, complex FS are associated with a small increase in the risk of death compared with simple febrile seizures.^[39] This finding was partly explained by pre-existing neurological abnormalities which could not be ascertained in this study.^[40] One report related sudden death with complex FS in a series of toddlers to developmental hippocampal pathology and possible nocturnal seizures.^[41]

CONCLUSION

Febrile seizures can cause morbidity in children, though benign in nature complex seizures are associated with hyponatremia and mortalities in this study. Hyponatremia was also associated with recurrence of seizures within the illness especially with presence of high fever. It is recommended that full electrolyte profile should be done in children with FS to ascertain risk of recurrence in Nigerian children.

Conflict of interest: None

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