Clinical, epidemiological and laboratory characteristics of children with febrile seizures

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ABSTRACT

Background: Febrile seizure is the most common type of seizure disorder that occurs in children aged 6-60 months. Recurrences are common. This study was conducted to evaluate the epidemiology, clinical profile and laboratory parameters of children presenting with febrile seizure in a teaching hospital.

Methods: This was a descriptive retrospective study among children presenting with febrile seizure admitted to KIMS, Bengaluru from March (2018-2019). Children between six months to five years were included in the study while patients with prior episodes of afebrile seizures, abnormal neurodevelopment and not meeting the age criteria were excluded. Patient’s demographic and clinical data were collected from the in-patient records and analysed.

Results: Among 60 children with febrile seizures were enrolled in our study with highest prevalence in males (58%) and amongst 13-24 months age group (37%). Majority (20%) presented in the monsoon season (June) and in the morning hours (43%). Simple febrile seizures and complex febrile seizures were observed in 60% and 40% respectively. Majority (73%) who developed first episode of seizure were below 24 months ago with mean age of 18.71±11.50 months. 42% had recurrence and was significantly associated with first episode of febrile seizures at age ≤1 year and family history of seizures. Upper respiratory tract infections were the commonest cause of fever. Anaemia and leucocytosis were seen in 72% and 70% cases respectively.

Conclusions: Febrile seizure was observed predominantly in children below two years, simple febrile seizure being the commonest. Recurrence was common and significantly associated with the first episode of febrile seizure at the age one year or below and family history. Majority had anaemia which showed that iron deficiency anaemia could be a risk factor. Leucocytosis was present in most which could be either due to underlying infection or due to the stress of seizure itself.

Keywords: Anaemia, Complex febrile seizure, Leucocytosis, Recurrence, Simple febrile seizure

INTRODUCTION

Febrile seizure is the most common type of seizures seen in 2-5% of children below five years of age and in which seizure is accompanied by fever, but without evidence of intracranial infection and acute electrolyte imbalance. Despite its benign nature, the febrile convulsion is one of the most common reasons for admission to paediatric emergency wards worldwide.

The American Academy of Paediatrics (AAP) defines febrile seizures as a seizure occurring in febrile normal children with axillary temperature greater than 38°C (100.4°F) between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures and who may/may not have a family history of febrile/seizures/epilepsy.1 Febrile seizures can be classified as either simple or complex.2 Simple febrile seizure which accounts for 80-85% of all
Febrile seizures is a generalized seizure (without focal features) which lasts less than 15 min and occurs only once during a 24-hour period of fever in a neurologically normal child.\(^3\)\(^-\)\(^7\) A complex febrile seizure has one or more of the following features; focal features during the seizure or is followed by neurological deficit or prolonged duration (>15 min) or recurrent within 24-hour or within the same febrile episode or the child has a previous neurological impairment.

The peak incidence of febrile seizure is between 12 and 18 months.\(^1\)\(^-\)\(^3\)\(^,\)\(^8\)\(^-\)\(^10\) The male-to-female ratio is approximately 1.6 to 1.\(^1\)\(^3\)\(^,\)\(^11\)\(^-\)\(^13\) Seasonal variation with regard to seizure incidence has not yet been fully understood. Studies have shown that febrile seizures tend to occur more in the winter months and are more common in the evening but some studies have shown that the majority of febrile seizures occur in the winter months but in the afternoon.\(^14\)\(^-\)\(^18\)

One-third of children who have a febrile seizure will have another one with another febrile illness. The younger the child is at the time of the first episode, the greater the risk is of recurrence. Approximately 50% of the recurrences occur within 6 months of the initial seizure; 75% occur within 1 year. The risk of recurrence of febrile seizures is related to various factors, including younger age group (<15 months), prolonged seizure duration, short time between the onset of fever and seizure, low degree of fever before their seizure and positive personal and family history of febrile seizure or epilepsy.\(^19\) Approximately one-third of children with febrile seizures have a positive family history.\(^20\) In most cases, febrile seizures occur within first day of the fever.\(^2\)\(^,\)\(^21\) Viral infection (80%) is the commonest cause of fever in febrile seizures.\(^22\) Viral upper respiratory tract infection, pharyngitis, otitis media, and gastroenteritis are other important causes of febrile seizures.\(^23\)\(^,\)\(^2\)

Iron deficiency anaemia may predispose to febrile seizures.\(^22\)\(^,\)\(^24\)\(^-\)\(^30\) Studies have also shown that the stress from fever or seizure results in leukocytosis with neutrophilic predominance following release of epinephrine.\(^31\)

Recurrence of seizure episodes and concern about epilepsy are major parental concerns regarding long term effects of febrile seizure. Attempts to identify factors associated with recurrence have been made and first episode of febrile seizure below 12 months, complex febrile seizure, family history and temperature below 40°C were found associated with the recurrence.\(^32\) However, few studies showed conflicting results.\(^33\)\(^,\)\(^34\)

Similarly, etiology of fever varies in various studies.\(^33\)\(^,\)\(^35\)\(^-\)\(^37\) Hence this study was conducted with objectives to evaluate demographic, clinical profile and laboratory parameters with an emphasis on recurrence of febrile seizures in children presenting to our teaching hospital.

**METHODS**

This was a descriptive retrospective study conducted from March 2018 to March 2019 among children admitted with febrile seizure to the Paediatric Intensive Care Unit of Kempegowda Institute of Medical Sciences Hospital and Research Centre (KIMS), Bengaluru. Records of all the patients with a diagnosis of febrile seizure based on standard definition were included. Patients with prior episodes of afebrile seizures, abnormal neurodevelopment and age below six months and above five years were excluded from the study. A recurrence of febrile seizure was defined as a subsequent febrile seizure during a new febrile period. Patient’s demographic and clinical data regarding type of seizure, duration, number of episodes, interval from onset of fever to seizure, past episodes of febrile seizure, family history of febrile seizure and epilepsy and cause of fever were obtained from the patient records. Lab investigation for each patient was guided by clinical examination. Lumb puncture for cerebrospinal fluid analysis was considered in all patients aged below 12 months with simple febrile seizure, patients aged 12-18 months after clinical decision and all patients with complex febrile seizure.

Manual checking and coding of data were undertaken before data entry commenced to clean the data and ensure consistency. Once entered, data were checked for any errors; any necessary checks with the original questionnaires were undertaken and corrected before further analysis.

All analyses were conducted using software SPSS 23 Version; Texas, USA. Frequency of the qualitative variables was presented in percentage. Value of continuous variables was presented as mean±SD. A chi-square test was used to test association between the factors and outcome variables. A p value <0.05 was considered as statistically significant.

**RESULTS**

Out of the total 86 admitted seizure cases, 60 children with febrile seizures were enrolled in our study as per the inclusion criteria which constituted 2% of the total 2960 paediatric admissions. Mean age of presentation was 21.43±11.95 months and the highest prevalence (37%) was seen among 13-24 months age group.

The youngest of the participant was 6 months of age and the oldest 51 months of age. Additionally, the study revealed age has an inverse relation with the prevalence of febrile seizure as the lowest prevalence (3%) was noted among ≥49 months age group (Figure 1).

Seizures were seen more in males (n= 35, 58.33%) which was more than half as compared to females (n= 25, 41.67%) (Figure 2) with male to female ratio 1.4:1.
Upper respiratory tract infections were the most common cause of febrile illness in this study which was seen in 21 (35%) of children followed by gastroenteritis 14 (23.3%) (Figure 3).

Maximum number of cases (n=12, 20%) presented to us during the monsoons (June) and were more common in the morning hours (n=26, 43.3%), and the least in February and April with only 1 case each (n=1, 1.66%) (Figure 4, 5).

Simple febrile seizure was seen in 36 (60%) children and complex febrile seizure was seen in 24 (40%) children. Generalized tonic-clonic seizure was the predominant type of seizure which was seen in 49 (81.7%) children and 11(18.3%) had focal seizures. About three-fourth (71.6%) of the children developed seizures within 24 hours of onset of fever (Figure 6).
Most of the children 40 (66.7%) had single episode of seizure per febrile episode. Whereas 12 (20%) children had two episodes, 8 (13.3%) children had three episodes of seizures in the present febrile episode (Figure 7).

Among 52 (86.7%) children had seizure for 5 to 10 minutes duration and 8 (13.3%) had seizure for 10 to 15 minutes. Temperature of ≥38°C was documented in 49 (81.67%) patients at presentation to the hospital and mean temperature was 38.3 (±0.8)°C.

The first episode of febrile seizure commonly occurred in the age group of 13-24 months (40%) followed by 6-12 months (33%) with the mean age of 18.71±11.50 months (Figure 8). 25 (41.7%) children had recurrence of febrile seizures in the past. 17 (28.3%) children had positive history of febrile seizure in other family members and 1 (1.66%) child had history of epilepsy in family. 11 (18.3%) children had both recurrence and family history of seizures.

Table 1: Laboratory investigations in children with febrile seizures.

<table>
<thead>
<tr>
<th>Lab Abnormality</th>
<th>Frequency (N=60)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>43</td>
<td>71.66</td>
</tr>
<tr>
<td>Leucocytosis</td>
<td>42</td>
<td>70</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>2</td>
<td>3.33</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>6.66</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>44</td>
<td>73.33</td>
</tr>
</tbody>
</table>

Haemoglobin, total leucocyte count, differential count, peripheral smear, serum electrolytes, serum calcium and blood sugar were done as clinically indicated. The abnormal laboratory findings are tabulated in Table 1.

Table 2: Association of various parameters with recurrence of febrile seizures.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Recurrence of febrile seizure</th>
<th>Total number</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>Number</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>62.8</td>
<td>37.2</td>
<td>0.44*</td>
</tr>
<tr>
<td>Family history of febrile seizure</td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>48</td>
<td>18</td>
</tr>
<tr>
<td>Seizure duration</td>
<td>Positive family history of seizure</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Negative family history of seizure</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>66.6</td>
<td>33.4</td>
<td></td>
</tr>
<tr>
<td>Temperature at admission</td>
<td>5 to 10 minutes</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>55.7</td>
<td>44.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 to 11 to 15 minutes</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 38 °C</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>61.2</td>
<td>38.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 38 °C</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>45.5</td>
<td>54.5</td>
<td></td>
</tr>
<tr>
<td>Seizure frequency</td>
<td>One</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>61.5</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More than one</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>52.4</td>
<td>47.6</td>
<td></td>
</tr>
<tr>
<td>Age category at first episode of febrile seizure</td>
<td>≤12 months</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;12 months</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>72.5</td>
<td>27.5</td>
<td></td>
</tr>
<tr>
<td>Interval between seizure and fever</td>
<td>≤10 hours</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>55.8</td>
<td>44.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10 hours</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>64.7</td>
<td>35.3</td>
<td></td>
</tr>
<tr>
<td>Type of febrile seizure</td>
<td>Simple febrile seizure</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>63.8</td>
<td>36.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complex febrile seizure</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05 significant

Anaemia was seen in 72% cases. Leucocytosis, leucopenia, neutrophilia was seen in 70%, 3.3%, 73.3% respectively in this study population. Out of 60 children, 22 (36.7%) children required lumbar puncture for cerebrospinal fluid analysis. 12 (20%) children had normal cerebrospinal fluid results while 10 (16.7%)
patients refused lumbar puncture despite the medical advice.

Table 2 describes association between patients’ conditions and recurrence of febrile seizure.

Recurrence of febrile seizure was observed in 25 (41.7%) patients. Among children with simple and complex febrile seizure, recurrence of febrile seizure occurred in 13 (36.2%) and 12 (50%) children respectively. The study revealed that the likelihood of recurrence of febrile seizure was associated with age at first episode. It was noted that the recurrence among the younger age groups 12 months or less were almost three-fourth (70%) in comparison with age group of more than 12 months (27.5%; p= 0.002). Furthermore, this study also revealed a statistical significance between the recurrence of febrile seizures and family history of seizures (61.2%) (p= 0.04). The study did not find any association between type of febrile seizure, sex, seizure duration, temperature at presentation, interval between seizure and onset of fever, frequency of seizure and the recurrence of febrile seizure. Recurrence was observed after mean duration of 2.71±0.09 months of last episode of febrile seizure.

**DISCUSSION**

Febrile seizure is a common neurologic disorder in children. In our study febrile seizures represented 2% of total paediatric admissions which was similar to other studies that showed the proportion 2-5% of total paediatric admissions.\(^{35,37}\) It predominantly occurred in children below 24 months of age in this as well as other studies.\(^{36}\) The mean age of children (21.43 ± 11.95 months) in this study was comparable to other studies.\(^{35,38}\) Male to female ratio was 1.4:1 which reemphasized previous studies that febrile seizure was more frequent in boys than girls.\(^{33,35,36,39}\) However, this study was hospital based and probable gender bias for health seeking behaviour might also be the limiting factors.

Simple febrile seizure (84% to 89%) is more common than complex febrile seizure (11% to 16%) in different studies worldwide.\(^{40,41}\) In this study 60% had simple febrile seizure and 40% complex febrile seizure. As described in previous studies, this study also showed that generalized seizure was the most frequent seizure, out of which majority of patients had generalized tonic clonic seizure. Majority (65%) of children in this study had single episode of seizure which was similar to previous studies.\(^{35,36,38,40}\) The seizure occurred after mean duration of 9.6 (±7.1) hours of onset of fever in this study while this duration varied in other studies from 16.5 (±21.3) hours to 2.2 (±1.8) days.\(^{35}\) About three-fourth (71.6%) of the children developed seizures within 24 hours of onset of fever.\(^{2,21,38}\)

Seasonal and diurnal variations in the occurrence of febrile seizures have been observed in studies from United States, Finland and Japan.\(^{15-18}\) In this study seizures were more prevalent in the month of June (20%) that is in the monsoon season and is more frequent in the morning hours (43.3%) followed by night (25%) unlike a study from Finland where seizures were more prevalent in winter months and evening\(^{15}\) and study from Iran showed that seizures occurred more in the afternoon and in winters.\(^{18}\)

Family history of seizure varied from 0.4% to as high as 20.6% of children with febrile seizure as reported in previous studies.\(^{33,35,45}\) In our study, family history of seizure was noted in almost one-third (30%) of patients which was similar to a study in Iran (28.8%). However, it should also be noted that parents may be unaware of their past episodes of febrile seizure and thus may confound the exact family history.\(^{52}\)

Cause of fever in children with febrile seizure varies in different studies depending on geographical location. The important viral or bacterial infection causes of febrile seizures as seen in various studies conducted in Iran were upper respiratory infection 42.3%, gastroenteritis 21.5%, otitis media infections 15.2%, pneumonia 8.7%, urinary infections 3.2%, roseola 2.0%, and other infections 12.8%.\(^{43}\) Upper respiratory tract infections (35%) were the commonest cause of fever in children in this study which was similar to other studies.\(^{35,36,39,44}\) Viral infections were presumed in majority of these children with upper respiratory tract infection based on clinical features and the course of illness. Acute gastroenteritis (23%) was the second commonest cause of fever in children in this study.

Biochemical, haematological investigations and lumbar puncture for cerebrospinal fluid were performed when indicated clinically as per guidelines.\(^{45}\)

The relationship between iron deficiency anaemia and febrile seizures has been suggested in several studies, although there are conflicting results regarding the role of iron deficiency anaemia in febrile seizures.\(^{46,47}\) A meta-analysis of 17 studies conducted from different countries suggested that iron deficiency anaemia was associated with an increased risk of febrile seizures in children. In our study, 72% of the patients were anaemic. Leucopenia, leucocenia, neutrophilia were seen in 70%, 3.3%, 73.3% cases respectively in our study. A study by Mohammad R Mohabbi et al revealed that changes in leucocyte counts appear more likely to be related to the length and underlying etiology of the fever than to the seizure itself.\(^{48}\)

Recurrence of seizure is one of the major concerns in children with febrile seizure. This study showed recurrence in 42% of children which was comparable to 37% in another study with the first episode of febrile seizure commonly occurring in the age group of 13-24 months (40%) followed by 6-12 months (33%) with the mean age of 18.71±11.50 months.\(^{49}\) Recurrence was observed after mean duration 2.71±0.09 months of last
febrile seizure in this study. Children with first episode of febrile seizure at an age one year or below was found to have significantly increased likelihood of recurrence. Recurrence has been associated with early age of onset, family history, and complex febrile seizure while another study correlates recurrence with low temperature at onset of seizure and duration of fever of <12 hours prior to onset of seizure.\textsuperscript{3,34,41,49} This study illustrated febrile seizure recurrence was associated with both age of onset of febrile seizure at one year or below (p value <0.002) and family history of seizures (p value <0.04) but significant association with sex, seizure duration, temperature at presentation, interval between seizure and onset of fever and type of seizure were not found. This study had inherent limitations being a hospital based study. Recall bias regarding history of febrile seizures in parents as well as exact duration of seizure and details of first episode of febrile seizure could not be minimized and these patients were not followed up to determine the risk of epilepsy.

Population based studies are needed to evaluate an exact incidence of febrile seizure in Indian children. Prospective studies with follow up of patients after first episode of febrile seizure would be of great value to identify factors determining the recurrence and its relation to future epilepsy in Indian population.

**CONCLUSION**

Simple febrile seizure was the most common type and febrile seizure predominantly affected children below two years of age. First episode of febrile seizure occurred in majority in the age group of 13 to 24 months age group. Three-fourth of the children had anaemia which showed that iron deficiency anaemia could be a risk factor for development of febrile convulsions. So evaluation of iron status is encouraged to be performed in children with febrile seizure. Majority of the children had leucocytosis from which we can deduce that leucocytosis could be either due to underlying infection or due to the stress of convulsion itself.

Recurrence of febrile seizure was common and was significantly associated with age of first episode at one year or below and positive family history of seizure. Hence it is recommended that parents of children with first episode of febrile seizure occurring at an age of one year or below be appropriately counselled regarding seizure recurrence and measures to be taken during seizure activity as well as explain the benign nature of illness; which might reduce parental anxiety during further episodes of febrile seizure.

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