Original Article

Risk Factors of Recurrence of Febrile Seizures in Children in a Tertiary Care Hospital in Kanpur: A One Year Follow Up Study

Navneet Kumar, Tanu Midha[1], Yashwant Kumar Rao[2]

Departments of Neurology and [2]Pediatrics, GSVM Medical College, Kanpur, [1]Department of Community Medicine, Government Medical College, Kannauj, Uttar Pradesh, India

Abstract

Background: Febrile seizures are commonly seen in children and about one-third of the children develop a recurrence of febrile seizures. **Objectives:** The main objective is to study the risk factors associated with recurrence of febrile seizures in Indian children. **Methods:** This prospective, longitudinal study was carried out in the Department of Pediatrics, GSVM Medical College, Kanpur. All children, 6 months to 5 years of age, attending the department from February 2015 to January 2016 presenting with first febrile seizures were included in the study and followed up for recurrence. **Results:** Of 528 children, 174 (32.9%) had recurrence and 354 (67.1%) had a single episode of febrile seizures. Recurrence was more in children <18 months (41.3%) as compared to children ≥18 months (24.1%). Children with temperature 101°F during the seizure had a recurrence rate of 52.5% while recurrence was seen in only 17.2% in children with temperature ≥105°F. There was a significant declining trend of recurrence with increase in temperature. Recurrence was significantly more common in children with a family history of febrile seizures (45.5%) as compared to those without family history (27.8%). Multiple logistic regression analysis revealed that younger age at onset of first seizure, lower temperature during the seizure, brief duration between the onset of fever and the initial seizure, and family history of febrile seizures were risk factors significantly associated with recurrence of febrile seizures in children. **Conclusion:** Younger age at first seizure, short duration of fever before the onset of first febrile seizure, lower temperature at onset, and family history of febrile seizures are risk factors of recurrence of febrile seizures in children.

Keywords: Children, febrile seizures, recurrence, risk factors

Introduction

Simple febrile seizure is defined as a short (<15 min) generalized seizure, not recurring within 24 h, that occurs during a febrile illness not resulting from an acute disease of the nervous system in a child aged between 6 months and 5 years, with no neurologic deficits and no previous afebrile seizures. The most common type of seizures seen in children are febrile seizures. They occur in around 2%–5% of all children and recurrence is seen in about one-third.[1,2]

In a study from Yelandur in rural South India, the prevalence of febrile seizures was found to be 3.28–5.71/1000.[3] Another study from Uttarakhand estimated the prevalence of 2.27/1000 population.[4]

Simple febrile seizure has been defined by The International League Against Epilepsy as "A short generalized seizure, of a duration of <15 min, not recurring within 24 h, 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 post-natal brain damage, with normal psychomotor development, and with no previous afebrile seizures). Fever may not be detected before the seizure, but it must be present at least in the immediate postacute period and be the symptom of a pediatric disease."[5] Complex febrile seizure (CFS) has been defined as "A focal, or generalized and prolonged seizure, of a duration of >15 min, recurring more than once in 24 h, and/or associated with postictal neurologic abnormalities, more frequently a postictal palsy (Todd's palsy), or with previous neurologic deficits."[5] If the CFS is characterized by a duration of >30 min, or by shorter serial seizures, without consciousness being regained at the interictal state, the disorder is named febrile status epilepticus.[5]

Children suffering from simple febrile seizures have almost the same risk of developing epilepsy as the general population (1%). However, children who have had recurrent febrile seizures are <12 months at the time of their first febrile seizure and have a family history of epilepsy are at increased risk of developing epilepsy (2.4%).[6] Children younger than 12 months at the time of their first simple febrile seizure have an approximately 50% probability of having recurrent febrile seizures.

There is also a theoretical risk of death during a simple febrile seizure as a result of injury, aspiration, or cardiac arrhythmia.[7]

Address for correspondence: Dr. Tanu Midha, Department of Community Medicine, Government Medical College, Kannauj - 209 732, Uttar Pradesh, India.
E-mail: tanumidha2001@gmail.com

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Currently, long-term therapy for prevention of recurrence of febrile seizures is not recommended. When parental anxiety related to febrile seizures is extreme, intermittent oral diazepam at the onset of febrile illness may be effective in preventing recurrence.

Several studies have revealed that environmental and genetic factors influence the recurrence of febrile seizures. Earlier only age at the time of the first occurrence was considered as the risk factor responsible for recurrence, but other factors have also been identified.[8] Higher risk has been seen in children with a family history of febrile seizures, family history of epilepsy, CFS during the first episode, and neurodevelopmental problems.[9] Increased risk of febrile seizures has also been reported after vaccination with diphtheria and tetanus toxoids and whole-cell pertussis vaccine and measles, mumps, and rubella vaccine (MMR).[7] Iron deficiency has also been associated with increased risk of febrile seizures. Identification of these risk factors, associated with recurrence of febrile seizures, in the child by thorough history taking, examination, and investigation, may be useful to counsel the parents and to allay their anxiety during future episodes.

Very few studies have been reported from India. Therefore, this study was conducted to assess the risk factors associated with recurrence of febrile seizures in Indian children.

Methods

Setting and design

It was a prospective, longitudinal study conducted in the Outpatient and Inpatient Department of the Department of Pediatrics, GSVM Medical College, Kanpur. All children 6 months to 5 years of age, attending the department from February 2015 to January 2016, presenting with first febrile seizures were included in the study and followed up to assess for recurrence. Ethical clearance was obtained from the Institutional Ethical Committee, GSVM Medical College, Kanpur.

Inclusion criteria

Study participants included children between 6 months and 5 years, presenting with seizure accompanied by fever, that is, a core body temperature (rectal temperature)[10] of 100.4°F or 38°C, without central nervous system infection whose parents had given written informed consent.

Exclusion criteria

Children with previous febrile seizures, unprovoked seizures, and children with intracranial infections were excluded from the study. Furthermore, those children whose parents did not give consent were excluded.

Unprovoked seizures are seizures occurring in the absence of precipitating factors and may be caused by a static injury (remote symptomatic seizures) or a progressing injury (progressive symptomatic seizures).[11]

Intracranial infection was diagnosed if (a) microorganisms were cultured and identified from the cerebrospinal fluid (CSF) and (b) diagnosis was made by the attending physician with at least one of the following: Increased white cells, elevated protein or decreased glucose on CSF examination, microorganisms seen on Gram stain of CSF, microorganisms cultured from blood, or positive antigen test of CSF, blood, or urine.[12]

Methodology

Written informed consent was obtained from the parents of children who were included in the study. They were interviewed using a predesigned and pretested questionnaire.

The questionnaire was administered by a single interviewer, who was a postgraduate student in the department of pediatrics, to all the participants included in the study. The questionnaire was translated into Hindi (local language), validated by professors of Hindi and English language and pretested before being administered.

The first part of the questionnaire comprised screening questions to verify that the child never had a previous febrile or unprovoked seizure. The interviewer himself determined the type of febrile seizure, type of seizure, and epilepsy class.

Thereafter, a thorough neurological examination was done. Motor and sensory examination was conducted. Higher functions were assessed. Walking and coordination were also examined. Electroencephalography (EEG), CSF, computed tomography, and magnetic resonance imaging (MRI) were done, as and when required, to assess the cause of the seizure.

Seizures were classified as complex if the onset was focal in nature or prolonged in duration or there was more than one seizure during the course of illness. Seizure accompanied by secondary generalization was considered as a focal seizure.

Focal seizures evolving into generalized seizures, most often with tonic–clonic convulsions, were classified as secondarily generalized seizures. These focal seizures, which were once limited to one hemisphere of the brain, progress to encompass the entire brain bilaterally.[13]

A seizure was considered as prolonged if the duration was >15 min. The duration of focal impaired awareness seizures is theoretically determined by visual analysis of EEG recordings by two observers. The duration is defined as the time of earliest sustained local or regional ictal activity until the termination of ictal activity either in all electrodes (global duration), or at the onset area (focal duration). However, for the present study, the duration of seizure was considered as the time from the onset of generalized or focal seizure activity to the termination of the respective ictal activity.[14]

Data were also collected about the current illness, including the duration of fever before the seizure (<1 h or >1 h), maximum body temperature recorded before or just after the seizure, and other details such as family history of febrile seizures and history of neurodevelopmental problems. Hemoglobin was estimated using Sahli's method and peripheral blood smear was examined to look for microcytosis and hypochromia. A child with hemoglobin <11 g/dl and microcytic and

hypochromic anemia was classified as having iron deficiency anemia. If the child had been immunized within 2 weeks of the seizure episode (first or recurrent), he was considered as having a positive history of vaccination. Temperatures taken at the hospital were recorded in degrees Fahrenheit using an analog mercury thermometer (Hicks). After the first visit, the parents were followed up at every 3 months to assess for further seizures. Every child was followed up for 1 year. The follow-up period was till February 2017.

Of the 1045 children, presenting with seizures, 242 had neurocysticercosis, 181 had meningoencephalitis, and the remaining 93 had cryptogenic unprovoked seizures. Only 528 children fulfilling the inclusion criteria were included in the study.

Statistical analysis

Data were compiled using Microsoft Excel and analyzed using SPSS version 22.0 (SPSS Inc. Chicago, Illinois, USA). Categorical variables were analyzed using percentages and Chi-square test. Multiple logistic regression analysis was used to identify risk factors for recurrence of febrile seizures. $P < 0.05$ was considered statistically significant.

Results

A total of 528 children, aged 6 months to 5 years, having febrile seizures, were included in the study. Of these, 174 (32.9%) had recurrence and 354 (67.1%) had only a single episode of febrile seizures. The mean age of the study participants was 35.3 ± 2.5 months.

Table 1 shows the factors associated with recurrence of febrile seizures in children. Around 35.5% of the female children developed recurrence as compared to 28.9% of the male children, but this difference was not statistically significant ($P = 0.116$). There was no association between recurrence of febrile seizures and religion of the child or history of neurodevelopmental disorders. Recurrence was more common in children <18 months (41.3%) as compared to children ≥18 months (24.1%) and this difference was statistically significant ($P < 0.0001$).

Around 56.4% of the children with duration of seizure ≥15 min developed recurrence as compared to only 43.6% of the children with duration of seizure <15 min and this difference was not statistically significant ($P = 0.075$). Among children with temperature 101°F during the seizure, recurrence was seen in 52.5%, there was a significant declining trend with increase in temperature and recurrence was seen in only 17.2% in children with temperature ≥105°F ($P = 0.001$). Recurrence was significantly more common in children with a family history of febrile seizures (45.5%) as compared to those without a family history of febrile seizures (27.8%) and in children with a family history of epilepsy (78.6%) as compared to those without a family history of epilepsy (31.7%). Recurrence of febrile seizures was not associated with type of seizure, history of vaccination, and presence of iron deficiency.

Table 2 shows multiple logistic regression analysis to identify risk factors for recurrence of febrile seizures. It was observed that younger age at onset of first seizure, lower temperature during the seizure, brief duration between the onset of fever and the initial seizure, and family history of febrile seizures were significantly associated with recurrence of febrile seizures in children. For children aged ≥18 months, the risk of recurrence decreased by 0.39 times as compared to children with age <18 months. Children with temperature 101°F during the seizure were at maximum risk of recurrence and the risk decreased by 0.34 times for every 1°F rise in temperature. Children with duration of fever ≥1 h were at 0.13 times lesser risk of developing recurrence as compared to children with duration of fever >1 h. Gender and family history of epilepsy were not significantly associated with recurrence of seizures.

Discussion

In the present study, recurrence of febrile seizures was observed in 32.9% children aged 6 months to 5 years. This was similar to the findings of Berg *et al*. who reported recurrence in 27.1% children.[15] Several researchers have observed that there is a 15%–70% risk of recurrence in the first 2 years after an initial febrile seizure.[1]

The present study revealed that younger age at onset of first seizure, lower temperature during the seizure, brief duration between the onset of fever and the initial seizure, and family history of febrile seizures were risk factors associated with recurrence of febrile seizures. In the present study, recurrence was seen more commonly in children <18 months (41.3%) as compared to children ≥18 months (24.1%). Annegers *et al.* also found that children younger than 12 months at the time of their first febrile seizure were more likely to have recurrence.[16] Berg *et al*. also observed that children <18 months of age had a higher risk of recurrence.

In the present study, children with a temperature of 101°F during the seizure had a recurrence of 52.5%, whereas recurrence observed in children, with temperature greater than or equal to 105°F, was 17.2%. There was a significant declining trend of recurrence of febrile seizures with higher temperature during the seizure ($P = 0.001$). A study from Nepal also reported that low temperature at the onset of febrile seizure ($P = 0.001$) was significantly associated with recurrence of febrile seizures.[17] Berg *et al*. also found that for every degree Fahrenheit rise in temperature, from 101°F (38.3°C) to ≥105°F (40.6°C), the risk of recurrence at 1 year declined from 35% to 30%, 26%, 20%, and 13% (P for trend = 0.024).

In our study, children with fever duration <1 h before the onset of first seizure had a significantly higher risk (57.3%) in comparison to those with fever duration ≥1 h before onset of the first seizure (35.8%). Similarly, in the study from Nepal, short duration of fever before onset of febrile seizure ($P = 0.026$) was also a risk factor for recurrence of febrile seizures.[17] This was in concordance with the findings of Berg *et al*. wherein for children with fever <1 h before the onset of first seizure,

Table 1: Factors associated with recurrence of febrile seizures

Risk factors	Children with nonrecurrent febrile seizures (*n*=354), *n* (%)	Children with recurrent febrile seizures (*n*=174), *n* (%)	Total children (*n*=528)	*P*
Gender				
Male	143 (71.1)	58 (28.9)	201	0.116
Female	211 (64.5)	116 (35.5)	327	
Age at first seizure (months)				
<18	159 (58.7)	112 (41.3)	271	<0.0001*
≥18	195 (75.9)	62 (24.1)	257	
Duration of fever (h)				
<1	47 (42.7)	63 (57.3)	110	<0.0001*
≥1	307 (64.2)	171 (35.8)	478	
Temperature (°F)				
101	19 (47.5)	21 (52.5)	40	0.001*
102	68 (63.6)	39 (36.4)	107	
103	89 (64)	50 (36)	139	
104	106 (68.4)	49 (31.6)	155	
≥105	72 (82.8)	15 (17.2)	87	
Family history of febrile seizures				
Present	73 (54.5)	61 (45.5)	134	0.00034*
Absent	281 (71.3)	113 (28.7)	394	
Duration of seizure (min)				
≥15	31 (56.4)	24 (43.6)	55	0.075
<15	323 (68.3)	150 (31.7)	473	
Type of seizures				
Simple	230 (67.6)	110 (32.4)	340	0.692
Complex	12 (15.8)	64 (84.2)	76	
Neurodevelopmental disorders				
Present	15 (88.2)	2 (11.8)	17	0.054
Absent	332 (65.9)	172 (34.1)	504	
History of vaccination				
Present	34 (59.6)	23 (40.4)	57	0.208
Absent	320 (67.9)	151 (32.1)	371	
Iron deficiency				
Present	173 (67.8)	82 (32.2)	255	0.706
Absent	181 (66.3)	92 (33.7)	273	
Family history of epilepsy				
Present	3 (21.4)	11 (78.6)	14	0.0002*
Absent	351 (68.3)	163 (31.7)	514	

*P<0.05 is significant

the recurrence rate was 44% and for children with fever ≥1 h before the onset of first seizure recurrence rate was 33%. Graves *et al*. also reported that an increased risk of recurrence was associated with children <18 months of age, children with a lower fever and lesser duration of fever before the onset of seizure, and those having a family history of febrile seizures.[1]

The findings of our study revealed that type of seizure, presence of neurodevelopmental disorders, and family history of epilepsy were not associated with recurrence. These corroborated with the observations by Berg *et al*.[15] However, Annegers *et al*. observed that children with a family history of epilepsy have a greater risk of recurrence of febrile seizures.[16]

In the present study, history of vaccination was not found to be significantly associated with recurrence of febrile seizures in children. A Cochrane review and a review of 530,000 children receiving MMR vaccine revealed that a small (1 or 2 febrile seizures per 1000 vaccinations) risk of febrile seizures was present during the first 2 weeks after immunization, but it was most probably due to fever resulting from the vaccine.[18,19] However, this may be true only for the first episode and vaccination does not significantly increase the risk of recurrence.

In our study, the presence of iron deficiency was not significantly associated with recurrence of febrile seizures in children. In another study, children with febrile seizures had almost twice the incidence of iron deficiency in comparison to febrile children who did not have seizures. However, iron deficiency has not been studied in relation to recurrence.[20,21] There are a few limitations of the present study. The duration

Table 2: Multiple logistic regression analysis of factors associated with recurrence of febrile seizures in children (*n*=528)

Factor	Beta coefficient	OR	95% CI lower limit	95% CI upper limit	*P*
Gender (reference=female)	−0.05	0.95	0.42	2.15	0.897
Age at first seizure (reference ≤18 months)	−0.93	0.39	0.17	0.94	0.037*
Temperature (Per °F)	−1.09	0.34	0.15	0.76	0.009*
Duration of fever (reference=1 h)	−0.99	0.36	0.13	0.99	0.040*
Family history of febrile seizures (reference=absent)	1.31	3.72	2.27	6.10	<0.001*
Family history of epilepsy (reference=absent)	0.25	1.29	0.13	12.19	0.820

**P*<0.05 is significant. Reference category for dependent variable is subjects with nonrecurrent febrile seizure. OR=Odds ratio, CI=Confidence interval

of follow-up was 1 year which might have led to missing out of episodes of recurrence in the study participants later on in life. Iron deficiency anemia was assessed using hemoglobin and peripheral blood smear, while an assessment of iron stores is required for more accurate estimation of iron deficiency.

In the present study, multiple logistic regression analysis revealed that younger age at onset of first seizure, lower temperature during the seizure, shorter duration between the onset of fever and the initial seizure, and family history of febrile seizures were significantly associated with recurrence of febrile seizures in children. In another study from South India also, risk factors for experiencing recurrent febrile seizures were the onset of seizures at a younger age, seizures with low-grade fever, CFS, multiple febrile seizures, and positive family history of febrile seizures or epilepsy.[3] Marudur *et al*. also observed that a temperature of <40°C during the febrile seizure (risk ratio [RR] = 2.29, 95% confidential interval [CI]: 1.35–3.89), history of febrile seizures among first-degree relatives (RR = 3.30, 95% CI: 1.25-8.08), age during the first febrile seizure of <12 months (RR = 2.40, 95% CI: 1.42–4.06), and duration of fever before the seizure of <1 h (RR = 4.62, 95% CI: 1.35–15.80) were significant risk factors for recurrent febrile seizures.[22] In a case–control study, Ridha *et al*. also reported that upon multiple logistic regression, younger age at onset of the first febrile seizure and shorter duration of fever before the first febrile seizure were significantly associated with recurrence of febrile seizures.[23]

Other studies have reported that the risk factors for experiencing subsequent epilepsy are preexisting developmental delay, positive family history of epilepsy, and CFS.[24,25] However, in a study from Columbia University, age at first seizure, abnormal development, temperature during the seizure, family history of febrile seizure, and family history of epilepsy were not significantly associated with the recurrence of febrile seizure epileptics.[26] MRI abnormalities and acute T2 signal at baseline were significantly associated with recurrence of febrile seizure epilepticus. This maybe because of the constitutional difference in the population and the fact that the outcome studied was recurrence of febrile status epilepticus not merely recurrence of febrile seizures.[26] Recurrent febrile seizures can adversely affect the quality of life of the family as the parents may experience anxiety and fear whenever a child gets fever. This fear is referred to as the "vulnerable child syndrome," which includes a compilation of behaviors that are thought to occur as a result of excessive parental anxiety.[27] This exaggerated parental fear of fever and febrile seizures can have negative consequences on daily family life, parental behavior, and parent–child interactions. This fear and anxiety can be allayed by proper education and counseling regarding febrile seizures. Parents and caregivers should be provided specific information about how to care for the child. For the physician, identification of risk factors of recurrence may lead them to consider intermittent oral diazepam at the onset of febrile illness or maybe even consider long-term prophylaxis. Further studies are needed with a follow up of longer duration to study the risk factors and prognosis of recurrent febrile seizures.

Conclusion

This study has revealed that younger age at onset of first seizure, lower temperature during the seizure, brief duration between onset of fever and initial seizure, and family history of febrile seizures were significantly associated with recurrence of febrile seizures in children. These risk factors should be kept in mind by the physician, while dealing with a child suffering from febrile seizures. Caregivers of children at high risk should be advised for long-term prophylaxis as well as increased vigilance of their child during every episode of fever so as to prevent recurrence.

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Conflicts of interest

There are no conflicts of interest.

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