Neurology Asia 2017; 22(3) : 203 – 208

Clinical characteristics of febrile seizures and risk factors of its recurrence in Chiang Mai University Hospital

Worawit Kantamalee *MD*, Kamornwan Katanyuwong *MD*, Orawan Louthrenoo *MD*

Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Abstract

Background & Objectives: Febrile seizures are the most common convulsive disorder in children under 5 years old. Among these children, some develop recurrent febrile seizures. The objective of this study was to describe clinical characteristics of children with febrile seizures and to identify risk factors for developing recurrent seizures. *Methods:* A retrospective study was conducted from January 2004 to December 2013 in Chiang Mai University Hospital. Infants and children between 6 months and 5 years of age who were diagnosed with febrile seizures were included in this study. Clinical characteristics of children and all factors associated with seizure recurrence were extensively reviewed using electronic medical records. *Results:* There were 335 cases included for analysis. The mean age at onset of febrile seizures was 1.85 ± 0.95 years; 64.78 % were males. Among 261 cases who presented with first episode of febrile seizures, 52 cases (19.92%) developed recurrent febrile seizures. Respiratory tract infections were the most frequent etiology of febrile illnesses. Younger age at onset and family history of febrile seizures were statistically significant predictors of developing recurrent febrile seizures (p = <0.001 and 0.02, respectively). After adjusting the confounding variables, similar findings were found from the multiple logistic regression analysis (p = 0.003 and 0.01 respectively). *Conclusion:* In this study, younger age at onset of first febrile seizure and family history of febrile seizures were found to increase the risk of the recurrence of febrile seizures.

Keywords: Febrile seizure, simple febrile seizure, complex febrile seizure, recurrent febrile seizure, epilepsy

INTRODUCTION

Febrile seizures are the most common convulsive disorder in infants and children. It has been reported that 1 in every 25 children in the general population will experience febrile seizures at least once during their childhood.[1] The International League Against Epilepsy (ILAE) has defined febrile seizures as seizure events in infancy or childhood featured with a temperature over 38°C without any evidence of acute electrolyte imbalances or central nervous system infection.[2]

Approximately one-third of children who have febrile seizures will develop seizure recurrence. The risk factors that can predict seizure recurrence is an issue of interest for physicians. In 1990, only age at the time of initial febrile seizure was firstly identified as a consistent risk factor of recurrent febrile seizures.[3] Later, family history of febrile seizures was also found to be a strong predictor of recurrent febrile seizures.[4] Until now, generally accepted risk factors include age of onset before 18 months, temperature close to 38°C, shorter duration of fever (less than 1 hour) before the seizure and family history of febrile seizures.[5] A family history of epilepsy and the peak temperature during the febrile seizure are still controversial for recurrence.[6,7]

When compared with previous studies, the risk factors for recurrence of febrile seizures and associated infectious diseases may be different in children in this region with histories of febrile seizures. Since febrile seizures in children often cause anxiety in parents, information regarding the natural risk factors would help parents to cope. Therefore, this study was conducted to determine characteristic features of febrile seizures and risk factors of recurrent febrile seizures in pediatric patients in Chiang Mai University Hospital.

METHODS

The pediatric patient registry database of Chiang Mai University Hospital from January 2004 to

Address correspondence to: Kamornwan Katanyuwong MD, Department of Pediatrics, Chiang Mai University Hospital, 110 Intavaroroj, Sripoom, Muang, Chiang Mai, Thailand 50200. Tel: 66-53-93-5412, Email: kkatanyu@gmail.com

December 2013 was searched retrospectively using ICD-10 "R560 Febrile convulsions" and enrolled in the study. Other ICD-10 codes related to other diagnoses, e.g. grand mal seizure or petit mal seizure, were not searched due to concern of overlapping data with the adult patients.

Eligibility

The hospital numbers of enrolled patients were acquired and the medical records were thoroughly reviewed by one reviewer. Cases with incomplete data or data loss, age less than six months and age six years or greater, central nervous system infection or electrolyte imbalances, prior non-febrile seizures and prior nervous system structural abnormalities were excluded from the study. The same hospital number with multiple outpatient visits or inpatient admissions was counted as a single patient under one study code. Every medical record was reviewed from the first to the last visit.

The information collected included clinical characteristics, risk factors and investigations. Clinical characteristics included age at initial febrile seizure, age at last follow-up, sex, febrile seizure types, temperature before and after febrile seizure, duration of fever before febrile seizure, duration of seizure and etiology of fever. Risk factors included prematurity, history of neonatal intensive care unit (NICU) admission, family history of febrile seizures, family history of epilepsy, day-care attendance, maternal alcohol consumption and smoking during pregnancy, developmental delay and other underlying diseases. Investigations included complete blood count, urinalysis, chest radiography, stool examination, cerebrospinal fluid profile if spinal tapping was done, serum and body fluid cultures and electroencephalogram (EEG). In case of recurrent febrile seizures, the information of an initial seizure was recorded and number of total seizures was counted to date. In some patients with recurrent febrile seizures whose initial febrile seizure could not be reviewed, the information of their first hospital visit was recorded instead.

Statistical analysis

The data were evaluated using SPSS statistical package, version 22 (SPSS, Chicago, IL). The percentage and mean ± standard deviation values were calculated for descriptive statistics. The Student t-test and Chi-square test were used for compare continuous and categorical data respectively. Logistic regression analysis was used for multivariate analysis. The risk was presented in mean difference and odd ratio (OR) in continuous and categorical data respectively along with confidence interval (CI). The level of statistical significance was set at $P< 0.05$.

RESULTS

This retrospective descriptive study included 335 cases, of whom 217 (64.78%) were male, with a male to female ratio of 1.8:1. The mean age at onset of febrile seizure was 1.85 ± 0.95 years. Among 261 cases who presented with first episode of febrile seizure, 52 cases (19.92%) developed recurrent febrile seizures. Simple febrile seizure was diagnosed in 276 cases (82.39%), while 59 cases (17.61%) were diagnosed as complex febrile seizure. Mean number of seizure episodes among 52 cases who presented with first febrile seizure with recurrence was 3.08 ± 1.74 episodes. Mean temperature at admission was 38.53± 0.97 degree Celsius. Mean time of fever before febrile seizure was 28.73 ± 28.48 hours. Mean duration of seizure was 2.60 ± 3.34 minutes. Subsequent epilepsy was found in 6 out of 335 cases (1.79%). Details of clinical characteristics of patients are shown in Table 1.

Associated symptoms of febrile illness together with family history are shown in Table 2. Positive first degree family history of febrile seizures was found in 84 (25.07%) cases. Twenty-five (7.46%) cases were born prematurely. Respiratory tract infection and acute gastroenteritis were the most frequent concomitant infections.

The distribution of risk factors for children with and without recurrent febrile seizures is shown in Table 3. We excluded 74 patients who already had previous recurrent febrile seizures prior to visiting our hospital. There were no statistically significant differences between cases with and without recurrent febrile seizures in respect to mean temperature at admission (p=0.12), mean time of fever before febrile seizures (p=0.32), mean duration of febrile seizures (p=0.59), gender (p=0.29), complex type of febrile seizures (p=0.44) and comorbid anemia (p=0.87)

Recurrent febrile seizures were significantly higher in cases with younger age onset of initial febrile seizures, in comparison to those who presented at older age, with a mean difference of -0.60 (p=<0.001). The recurrence rate of febrile seizures was also significantly higher in cases with positive family history of febrile seizures (35.3%), compared with those without such a family history (64.7%) with odds ratio of 2.17 (p=0.02). Additionally, according to the results of

Table 1: Clinical characteristic of febrile seizures (n=335)

	N (%)
Age at onset (yr), mean ± SD	1.85 ± 0.95
Gender	
Male	217 (64.78)
Female	118 (35.22)
First or recurrent episodes	
First FS without recurrence	209 (62.39)
First FS with recurrence	52 (15.52)
Recurrent FS	74 (22.09)
Characteristics of FS	
Simple FS	276 (82.39)
Complex FS	59 (17.61)
Mean number of FS episodes, mean ± SD	
First FS with recurrence	3.08 ± 1.74
Mean temperature at admission, mean ± SD	38.53 ± 0.97
Mean time of fever before FS (hr), mean ± SD	28.73 ± 28.48
Mean duration of FS (min), mean ± SD	2.60 ± 3.34
Median (range)	2 (0.1-30)
Subsequent epilepsy	6 (1.79)

FS = febrile seizures; SD = standard deviation.

Table 2: Family history and associated symptoms of children with febrile seizures (n=335)

	N (%)
Family history of FS	
Positive	84 (25.07)
Negative	249 (74.33)
History of prematurely born	25 (7.46)
First-born child	225 (67.16)
Comorbid developmental problems	12 (3.58)
Comorbid anemia	71 (21.2)
Associated symptoms	
Upper respiratory tract infection	209 (62.39)
Acute gastroenteritis	41 (12.24)
Pneumonia	17 (5.07)
Acute otitis media	13 (3.88)
Urinary tract infection	12 (3.58)
Occult bacteremia	9 (2.69)
Acute bronchitis	7 (2.09)
Viral croup	3 (0.89)
Others	9 (2.69)
Unknown	14 (4.18)

FS = febrile seizures.

Table 3: Risk factors of recurrent febrile seizures (n=261)

	Febrile seizures with recurrence (n=52)	Febrile seizures without recurrence (n=209)	Mean difference (95%CI)	p
Age at onset (y), mean (SD)	1.23 (0.65)	1.83 (0.89)	-0.60 (-0.82, -0.39)	<0.001
Mean temperature at admission, mean (SD)	38.37 (0.83)	38.61 (0.99)	-0.23 (-0.53, 0.06)	0.12
Mean length of fever before FS (h), mean (SD)	25.62 (30.32)	30.07 (28.69)	-4.46 (-13.31, 4.40)	0.32
Mean duration of FS (min), mean (SD)	2.79 (2.87)	2.52 (3.28)	0.27 (-0.71, 1.24)	0.59
	Febrile seizures with recurrence (n=52)	**Febrile seizures without recurrence** (n=209)	**Odds ratio (95%CI)**	**P**
Gender, n (%)				
Male	30 (57.7%)	137 (65.6%)	0.72 (0.39, 1.33)	0.29
Female	22 (42.3%)	72 (34.4%)		
Characteristics of first FS, n (%)				
Complex FS	8 (15.4%)	42 (20.1%)	0.72 (0.32, 1.65)	0.44
Simple FS	44 (84.6%)	167 (79.9%)		
Family history of FS, n (%)				
Positive	18 (35.3%)	42 (20.1%)	2.17 (1.11, 4.22)	0.02
Negative	33 (64.7%)	167 (79.9%)		
Comorbid anemia, n (%)				
Yes	12 (23.1%)	46 (22.0%)	1.06 (0.52, 2.19)	0.87
No	40 (76.9%)	163 (78.0%)		

CI = confidence interval; FS = febrile seizures; SD = standard deviation.

multivariate logistic regression analysis (Table 4), younger age at onset of febrile seizures (Adjusted OR= 2.88, 95%CI= 1.43-5.79, p= 0.003) and family history of febrile seizures (Adjusted OR= 2.38, 95%CI = 1.19-4.75, p= 0.01) were statistically significant risk factors of recurrent febrile seizures.

DISCUSSION

In this study, we found similarities and differences of characteristic of patients with febrile seizures as compared to previous reports. In our study, the mean age at onset of febrile seizure was 1.85 ± 0.95 years which is similar to the results of the studies by Esmaili *et al*., and Hussain *et al*., who reported age of onset at 22.58 ± 15.4 and 22.58 ± 12.50 months respectively.[8,9] The male was predominant in our study (64.78 %), which is similar to the findings of a study conducted by Habib *et al*.[10] In this study, 82.39 % of the patients had simple and 17.61% had the complex

Table 4: Risk factors of recurrent febrile seizures from multiple logistic regression analysis

	B	S.E.	Adjusted OR	95%CI	p
Younger age	1.06	0.36	2.88	1.43, 5.79	0.003
Lower temperature	0.23	0.33	1.26	0.67, 2.38	0.48
Male gender	-0.42	0.33	0.66	0.34, 1.25	0.20
Positive family history of febrile seizure	0.87	0.35	2.38	1.19, 4.75	0.01

CI = confidence interval; OR = odds ratio; SE = standard error.

form of febrile seizures. This is also similar to the findings of Esmaili *et al*.[8] Our study showed the mean temperature at admission of 38.62 ± 1.07°C which is similar to the findings from Esmaili's study which found the mean temperature at admission of 38.2 ± 1.32 °C. In our study, 25.07% of affected children had positive family history of febrile seizures, while other studies concluded differently.[9,11,12] This could be affected by genetic variation and the size of population studies. The main etiology of fever in this study was upper respiratory tract infection (62.30%), followed by acute gastroenteritis (12.24%) which is the same as the finding in Esmaili *et al*. and Hussain *et al*'s studies.[8,9] In contrast, mean time of fever in our study which was 28.73 ± 28.48 hours which is different from Hussain *et al*. who revealed 17.68 ± 12.09 hours.[9] This was probably due to aberrancy in history taking in our study because time was recorded in days. Among 335 patients, we found 6 cases with subsequent epilepsy. Although febrile seizures in childhood are generally benign with good clinical outcomes, recurrence affected one-third of cases studied.[3]

Many studies mentioned that the family history of febrile seizures was an important risk factor and associated with a 50-100 % increase in the risk of recurrent febrile seizures.[4,6] Approximately 25-40 % of children with febrile seizures had a positive family history of febrile seizures; the risk of developing febrile seizures among their siblings was reported as 9-22 %.[13,14] Our study revealed that a positive family history was significantly higher in children with recurrent febrile seizures, compared with those without recurrent febrile seizures. (Adjusted OR = 2.38, 95%CI 1.19-4.75). This result is similar to many studies in the past.[3-6]

Worldwide literature showed the major role of young age in susceptibility to febrile seizures.[3-6] Van *et al*.'s study in 1998 proposed that febrile seizures will develop if the temperature is far beyond the individual seizure threshold. Specifically, as the child grows older, the threshold for seizure became higher.[15] Most studies about the risk factors of recurrent febrile seizures agreed that low age at onset of initial febrile seizures increased the risk of recurrent febrile seizures. In our study, a child with recurrent febrile seizures had significantly lower age at onset compared with those without recurrent febrile seizures. (Adjusted OR = 2.88, 95%CI 1.43-5.79).

El-Rhadi *et al*. found that low temperature at the onset of the initial febrile seizure was an important risk factor in recurrent febrile seizures. Many studies showed similar findings.[3-6,16] In 2002, Berg described that children who present with seizures in response to a low degree of fever (<39°C) have a lower threshold and, therefore, have seizures with less provocation than children who require a higher degree of fever.[17] In our study, the temperature at onset of febrile seizure was lower in the patient with recurrent seizures compared to those without recurrence. However, this finding did not reach statistical significance. There are also studies which did not find temperature to be risk of recurrence.[18,19]

The duration of fever before developing febrile seizures was an important risk factor for recurrence of febrile seizures. The shorter the duration of fever prior to the seizures, the greater the risk for recurrence.[7] Pavlidou *et al*. found that recurrence rates of febrile seizures were significantly higher for cases with a febrile seizure within the first 12 hours of the febrile episode, compared with the between 12 and 24 hours.[6] Our study did not find the duration between fever and seizure as a significant factor to seizure recurrence.

Although our investigation has reached its aim, there are some limitations. Being a retrospective study, information could not be reviewed in every aspect. Initial febrile seizures information of 74 out of 335 patients (22.09%) with recurrent febrile seizures were unobtainable and could not be analyzed.

In conclusion, our study found family history of febrile seizures and younger age at initial febrile seizures to be significant risk factors for recurrent febrile seizures. However, we did not find seizure at low temperature or short period between fever and seizure to be risk factors for recurrence of febrile seizures. Knowing these risk factors of recurrent febrile seizures could help physician to identify those children who are at high risk for recurrence and to educate the parents regarding future care.

DISCLOSURE

Financial support: None

Conflicts of Interest: None

REFERENCES

1. Siqueira LF. Febrile seizures: update on diagnosis and management. *Rev Assoc Med Bras (1992)* 2010; 56(4):489-92.
2. Oka E, Ishida S, Ohtsuka Y, Ohtahara S. Neuroepidemiological study of childhood epilepsy by application of international classification of epilepsies and epileptic syndromes (ILAE, 1989). *Epilepsia* 1995; 36(7):658-61.

3. Berg AT, Shinnar S, Hauser WA, Leventhal JM. Predictors of recurrent febrile seizures: a metaanalytic review. *J Pediatr* 1990; 116(3):329-37.
4. Annegers JF, Blakley SA, Hauser WA, Kurland LT. Recurrence of febrile convulsions in a population-based cohort. *Epilepsy Res* 1990; 5(3):209-16.
5. Berg AT, Shinnar S, Darefsky AS, *et al*. Predictors of recurrent febrile seizures. A prospective cohort study. *Arch Pediatr Adolesc Med* 1997; 151(4):371-8.
6. Pavlidou E, Tzitiridou M, Kontopoulos E, Panteliadis CP. Which factors determine febrile seizure recurrence? A prospective study. *Brain Dev* 2008; 30(1):7-13.
7. Shinnar S, Glauser TA. Febrile seizures. *J Child Neurol* 2002; 17(Suppl 1): S44-52.
8. Esmaili Gourabi H, Bidabadi E, Cheraghalipour F, Aarabi Y, Salamat F. Febrile seizure: demographic features and causative factors. *Iran J Child Neurol* 2012; 6(4):33-7.
9. Hussain S, Tarar SH, Moin Ud Din S. Febrile seizrues: demographic, clinical and etiological profile of children admitted with febrile seizures in a tertiary care hospital. *J Pak Med Assoc* 2015; 65(9):1008-10.
10. Habib Z, Akram S, Ibrahim S, Hasan B. Febrile seizures: factors affecting risk of recurrence in Pakistani children presenting at the Aga Khan University Hospital. *J Pak Med Assoc* 2003; 53(1):11-7.
11. Ashrafzade F, Hashemzadeh A, Malek A. Acute otitis media in children with febrile convulsion. *Iran J Otorhinolaryngol* 2002; 16(35):33-9.
12. Hosseini Nasab A, Dai pariz M, Alidousti K. Demographic characteristics and predisposing factors of febrile seizures in children admitted to Hospital No. 1 of Kerman University of Medical Sciences. *J Med Counc Islam Repub Iran* 2006; 24(2):107-12.
13. Fetveit A. Assessment of febrile seizures in children. *Eur J Pediatr* 2008; 167(1):17-27.
14. Offringa M, Bossuyt PM, Lubsen J, *et al*. Risk factors for seizure recurrence in children with febrile seizures: a pooled analysis of individual patient data from five studies. *J Pediatr* 1994; 124(4):574-84.
15. van Stuijvenberg M, Steyerberg EW, Derksen-Lubsen G, Moll HA. Temperature, age, and recurrence of febrile seizure. *Arch Pediatr Adolesc Med* 1998; 152(12):1170-5.
16. el-Radhi AS, Withana K, Banajeh S. Recurrence rate of febrile convulsion related to the degree of pyrexia during the first attack. *Clin Pediatr (Phila)* 1986; 25(6):311-3.
17. Berg AT. Recurrent febrile seizures. In: Baram T, Shinnar S, eds. Febrile seizures. New York: Academic Press; 2002: 7-52.
18. Rantala H, Uhari M. Risk factors for recurrences of febrile convulsions. *Acta Neurol Scand* 1994; 90(3):207-10.
19. Tarkka R, Rantala H, Uhari M, Pokka T. Risk of recurrence and outcome after the first febrile seizure. *Pediatr Neurol* 1998; 18(3):218-20.