RECURRENCE OF FEBRILE SEIZURES IN YAZD SHAHID SADOUGHI HOSPITAL

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Abstract

Objective

Febrile seizure is the most common problem in pediatric neurology that occurs in 3-4 % of children. The purpose of this study was to determine febrile seizure recurrence frequency and to evaluate its risk factors.

Materials & Methods

In a descriptive prospective study, 139 children (6 months to 6 years) with first febrile seizure were admitted to Yazd Shaheed Sadoughi Hospital between March 2004 and August 2005 and were followed up for at least 15 months for febrile seizure recurrence.

Results

Seventy six boys and 63 girls with a mean age of 2.03 ± 1.21 years were followed up for 25.1 ± 5.5 months.

About 30% of them had complex febrile seizures and 37.4% had febrile seizure recurrence with a mean recurrence time of 6.7 ± 5.9 months. About 65% of the children younger than one year and 30% of those older than one year had febrile seizure recurrence. (P value= 0.0001)

Recurrence of seizure was seen in 63% of those who had seizure within an hour from the onset of fever and in 33% of those who had seizure after one hour from the onset of fever. (P value = 0.005)

Seizures in children younger than one year old and seizures occurring in association with a fever lasting less than an hour were risk factors of febrile seizure recurrence.

Conclusion

Febrile seizure is more disturbing in children younger than one year old. Antipyretic usage was not effective in preventing seizure recurrence but may reduce discomfort and is reassuring.

Keywords: Febrile Seizure, Recurrence, Risk factors

Introduction

Febrile seizure (FS) is the most common type of childhood seizures(1). It is also a common cause of pediatric admission and parental concern.

Based on population studies, FS cumulative incidence is 2-5% in Western Europe and the USA. The global incidence varies between 0.35% - 1.5% in China to 14%in Guam(2-4). Data from developing countries are limited, possibly because it may be very difficult to differentiate simple FS from acute symptomatic (infective) seizures, particularly if due to falciparum malaria infection(4).

International League Against Epilepsy defines FS as a seizure occurring in

association with a febrile illness in the absence of CNS infections or an acute electrolyte imbalance in children older than one month without prior afebrile seizures(4). This definition is similar to the one adapted earlier by the NIH Consensus Conference in 1980 while according to Berg, Febrile seizures occur between 6 months and 6 years of age by definition(5). FS is rare before 9 months and after 5 years of age (6) The child may be neurologically normal or abnormal.

Febrile seizures are further classified as simple and complex. A febrile seizure is complex if it is focal or focal findings are present during the postictal period, is prolonged more than 10 -15 minutes or is multiple (occurrence of more than one seizure during the febrile illness)(1).

Of all first FS, between 9% and 35% are complex (1,4). This wide variation may reflect the difficulties in differentiating simple from complex FS, and perhaps even differentiating FS from afebrile seizures(4).

One major concern in dealing with first FS is the risk of recurrence. It ranges from 21% to 43% in different studies (7,8,9).

Risk factors for recurrence after first FS, based on different studies, are as follows:

- 1. Age under one year (1, 2,4 & 9 -20)
- 2. Family history of febrile seizures (1, 2, 4, 8 -15 & 17-23)
- Seizure in temperatures below than 40° C (1, 2, 4, 10-14, 17-19, 21)
- 4. FS within an hour of the recognized onset of fever (1, 2, 12, 13)
- 5.Complex features (1, 2, 7, 9, 10, 12, 15, 16, 23): prolonged(24), multiple (4,11), focal(17)
- 6. Family history of epilepsy (2, 13-17)
- 7. Male sex (7)
- 8. Parental consanguinity (16)
- 9. Attendance at day care centers (2,8)
- 10. Recurrent febrile seizure (25)

The most consistent risk factors are the first two. One of the most important risk factors is being younger than one year at first FS. Half of the children with onset in the first year and 28% with onset after first years of age experience recurrence. Recurrence decreases to 10% with onset after 3 years (10, 11, 26).

Neurodevelopmental abnormality is not associated with

increased risk of recurrence(1).

Simple FS, especially in a child older than 12 months, is considered as a benign disease which requires neither specific tests [laboratory test, lumbar puncture, neuroimaging (CT or MRI), EEG], nor specific treatment(1), but complex FS is accompanied by further complications such as meningitis (1,27), recurrent FS (1, 2, 6, 7, 9, 10, 12, 15, 16, 23), subsequent epilepsy (1, 2, 4, 9, 14, 25) and status epilepticus (1).

Preventing or aborting prolonged febrile seizures to prevent status epilepticus with its attendant complications, however, remains a rational goal. ²⁵ Diazepam given orally or rectally at the time of the onset of a febrile illness reduces the probability of a recurrent FS and is indicated particularly in children at risk of prolonged or multiple FS or in those who live far from medical care or to allay familial anxiety. ¹Prophylatic daily anticonvulsant should be considered in infants with an abnormal neurological exam or developmental delay, complex febrile seizure with a positive family history of epilepsy and frequent and prolonged FS (26).

Multiple recurrences of FS predispose a child with FS to subsequent epilepsy(27-29).

The purpose of this study was to determine the recurrence rate of febrile seizures in children and to evaluate risk factors for recurrence in Yazd, a central city in Iran.

Materials and Methods

In a descriptive prospective study, 139 children (6months to 6years) with first febrile seizure were admitted to Yazd Shaheed Sadoughi Hospital between March 2004 and August 2005 and were followed up for 15-36 months for seizure recurrence. We made use of Berg definition for the age range of 6 months - 6 years in FC. Children with a history of afebrile seizure, evidence of central nervous infection, shigellosis encephalopathy and electrolyte abnormalities were excluded. Maximum temperature was defined as the highest rectal temperature recorded during the period of admission. The patient's characteristics, i.e., sex and age at the time of febrile seizure, type and duration of the seizure, the first presentation as being a simple or a complex febrile seizure, positive family history of febrile/afebrile seizures in the first and second degree relatives, duration of fever, developmental status, and maximum temperature were reviewed. The developmental status of the patient was assessed by a pediatrician and a pediatric neurologist based on Denver Developmental screening test. Data was analyzed using SPSS.15 statistical software. Unpaired t test and chi-square test were used to compare continuous and categorical variables, respectively, between groups with and without the recurrence of febrile seizure. Risk factors were initially examined by univariate analysis. Rate ratios were calculated for individual risk factors with a 95% confidence interval. Multivariate Cox regression analysis was used to examine the risk of recurrence after adjustment for individual risk factors. The Kaplan-Meier method was used to calculate probability of recurrence during the follow-up period. Statistical significance was taken as P < 0.05.

This study was approved by the ethic committee of Shaheed Sadoughi University of Medical Sciences, Yazd, Iran.

Results

Seventy six boys and 63 girls with a mean age of 2.03 \pm 1.21 years were followed up for 25.1 \pm 5.5 months. The male/female ratio was 1.2/1. Sixty-seven percent (n = 93) of them presented with simple febrile seizure whereas 33% (n = 46) presented with complex features. Among those with complex febrile seizures, 23 had multiple convulsions within 24 hours whereas 9 had focal features and 14 had prolonged convulsion. Number of first febrile seizure per age was as follows: < 1year (29), 1-2 years (63), 2-4 years (39) and > 4 years (8). Of all seizures, 66 % were in children younger than two and 6 % occurred in children older than four years.

Mean seizure duration was 8 ± 5.6 minutes in children younger than one year and 6.7 ± 5.3 minutes in those older than one year. Seizure was more prolonged in those <1 year (P value= 0. 04).

Fifty two patients had recurrent febrile seizures with a mean recurrence time of 6.7 ± 5.9 months. The overall recurrence rate was 37.4% by the Kaplan-Meier method. Cumulative recurrence was 11.5% by one month, 67.3% by six months, 88% by one year and 94% by 18 months. Recurrence rate displayed no further increasing trend by 2 years after the first episode, indicating that febrile seizure is unlikely to recur if a child does not experience any recurrence in 2 years after the first febrile seizure.

Of the 52 who experienced recurrence, 67% (35/52) had one, 23% (12/52) had two, and 10% (5/52) had more than two episodes of recurrence.

Sixty five percent (19/29) of the children younger than one year and 30% (33/110) of those more than one year had febrile seizure recurrence (P value= 0.0001).

In those <1 year, 48% (14/29) had one, 14% (4/29) had two, and 3.4 % (1/29) had more than two episodes of recurrence. In 1 – 2 year old children, 22% (14/63) had one, 9.5% (6/63) had two, and 4.8% (3/63) had more than two episodes of recurrence. In 2 - 4 year old children, 18 % (7/39) had one, 5% (2/39) had two, and 2.6 % (1/39) had more than two episodes of recurrence. In other words, In >1year old children, 19 % (21/110) had one, 7.2 % (8/110) had two, and 3.6 % (4/110) had more than two episodes of recurrence the number of the episodes of recurrence was more in those <1 year (p = 0.04).

Recurrence of seizure was seen in 63% of those who had seizure within an hour from the onset of fever and in 33% of those who had seizure after one hour from the onset of fever (P value = 0.005).

Thirty two cases of simple FS (34%) and 20 cases of complex FS (43%) had recurrent FS (P value=0.298).

Forty percent (34/86) of the children who used antipyretic in other febrile episodes and 34% (18/53) of those without antipyretic use had febrile seizure recurrence. Statistical analysis showed that antipyretic usage was not effective in preventing febrile seizure recurrence (P value = 0.5).

Mean recurrence time in different age groups is shown in Table 1. It can be seen that in children older than 4 years, FS recurs later (P value = 0.014).

Six children had neurodevelopmental delay (NDD) among whom occurrence of the first FS in the first year of life was seen in two while four others experienced FS between 1 and 2 years of age. These four patients had recurrence of FS. Two of them (33% of NDD) had one episode of recurrence and 33% (2/6) or the other two had two episodes. Twenty five percent (33/133) of the children with a normal developmental status showed one, 7.5% (10/133) showed two, and 3.7% (5/133) showed more than two episodes of recurrence. The two groups were not significantly different in this regard (P value = 0.224).

Developmental status of the children did not change in the end of the follow up period.

Subsequent epilepsy occurred in 50% (3/6) of the children with NDD and 4.5% (6/133) of the children without NDD and the frequency of subsequent epilepsy in NDD patients was higher (P value = 0.0001).

Table 2 demonstrates some data regarding the use of prophylactic drugs (daily phenobarbital or diazepam in the fever episode) in our patients. However, analysis of such data does not seem to be logical because methods of selecting patients are not universal and antiepileptic treatment is prescribed in complicated FS. Therefore, randomized clinical trials should be done in these situations.

Subsequent epilepsy was seen in 9 children. About 13.5% (7/52) of the children with recurrent FS and 2.3% (2/87) of those without recurrent FS suffered from

subsequent epilepsy. Frequency of epilepsy was higher in children with recurrent FS (P value = 0.01).

Univariate analysis of other factors is showed in Table 3. Sex, seizure type, FS type, fever height, neurodevelopmental status, positive family history of febrile seizure or epilepsy, seizure duration and EEG result were not related to febrile seizure recurrence.

Multivariate analysis disclosed that two factors were statistically significant: seizure in children younger than one year old and seizures occurring in association with a fever lasting less than an hour and they remained significant in Cox regression analysis. The rate ratio (RR) was 1.6 (95% confidence interval [CI] = 1.2 - 2.23 and P value = 0.0001) for early age of onset and 1.7 (95% CI= 1.45 - 2.23, P value = 0.02) for fever duration of less than one hour.

Age group	Total number	Number of recurrent FS	mean recurrence time (mo) ± SD
< 1 years	29	19	5.57± 4.7
1 – 2 years	63	23	6.09± 5.4
2-4 years	39	10	10.7±8.3
>4 years	8	0	0

Table 1. Comparison of mean recurrence time in different age groups

Table 2. Frequency of febrile seizure recurrence (in numbers) based on prophylactic drugs

Drug use Febrile seizure recurrence	No drugs	Diazepam during fever	Continuous phenobarbital	Total
Without	62	15	10	87
With	42	1	9	52
Total	104	16	19	139

Factor		Recurrence	No Recurrence	P Value	
A second Constanting	< 1year	19	10	0.0001	
Age at first seizure	> 1year	33	77		
Fever duration	< 1 hour	12	7	0.01	
rever duration	> 1 hour	40	80		
Sex	Male	24	52	0.119	
50%	Female	28	35		
Seizure in T <40°c	Yes	51	84	0.6	
	no	1	3		
Positive family history of FS in 1 st -2 nd degree relatives	Yes	13	15	0.27	
	No	39	72		
Positive family history of epilepsy in 1 st -2 nd degree	Yes	10	11	0.294	
relatives	No	42	76		
1 1 1 1 1	Yes	4	2	0.13	
developmental delay	no	48	85		
Seizure duration>10min	Yes	8	6	0.269	
	No	44	81		
Seizure type	Generalized	50	80	0.45	
	Focal	2	4		
	Secondary generalized	0	3		
	Normal	18	13	0.46	
EEG results	Nonspecific abnormal	22	11		
	Epileptic abnormality	3	4		

Table 3. Risk factors for recurrence of febrile seizure using univariate analysis

Discussion

The purpose of this study was to determine febrile seizure recurrence frequency and to evaluate its risk factors. In this study, Boys were affected slightly more than girls which supports other studies (1, 2, 4, 22 & 30-34).

One third of our patients had complex febrile seizures but in other studies, this rate varies between 6.7% and 35% (1, 4, 23, 24, 30 & 34 - 36). Possible explanations for this variety are ethnical and geographic differences, better diagnosis of partial seizures, methods of selecting patients, etc.

In the present study, seizures were more prolonged in infants (<1 year) that is similar to the results of a study by Farwell(35).

In this study, 13.7% of the children experienced their seizure either before or within 1 hour of the onset of fever which is lower than that of the Berg's study (21%) (18). On the other hand, FS occurred in spite of full dose use of antipyretic in 62% of the patients and therefore administration of antipyretic had no effects on febrile seizure recurrence which is in agreement with other

studies indicating that prophylactic antipyretic is not recommended to reduce FS recurrence rate(3, 37-40). The recurrence rate of febrile seizure in the present study was 37% that is similar to some other studies (1, 2, 4, 11, 12, 15, 25, 41); however, this rate varies between 15% and 48% (7, 8, 9, 12, 21) Possible explanations for this difference are the follow-up duration, ethnical and geographical differences, methods of selecting patients and the sample size.

Onset of febrile seizure at a young age is reported to be the most consistent risk factor for febrile seizure recurrence in some studies (1, 2, 4, 6, 9 - 20). In this study, 65% of the children younger than one year experienced febrile seizure recurrence. This figure is more than 50% in other studies (1, 10, 30). In one study, this rate was 73% (14). More prolonged seizures in infants may be a possible explanation for the results of our study.

In the present study, EEG results had no value in predicting the recurrence of febrile seizure as in other studies (2, 11, 42, 43) and it is recommended that EEG should be done in children with complex febrile seizures who have a recurrence without fever or in children with recurrent febrile seizures who exhibit developmental delays or neurologic deficits(1,44). In this study, seizure within an hour of the recognized onset of fever was one of the risk factors for FS recurrence, which is in agreement with other studies (1, 10.30.40). In our study, complex FS was not associated with increased risk of FS recurrence which is in compliance with other studies (1,17,18,20,21,28) but does not agree with some other studies(1, 2,6,7, 9,10,12,15,16,23). Possible explanations for this discrepancy are the number of the patients, methods of selecting patients, better diagnosis of partial seizures, etc.

Seizure in temperatures lower than 40 $^{\circ}$ c was not a risk factor of FS recurrence in the present study which does not agree with other studies (1, 2, 4, 10 -14, 17-19, 21).

Gender was not associated with increased risk of FS recurrence in this study which supports pediatric textbooks(1).

In this study, NDD was not a risk factor of FS recurrence which is in compliance with other studies (1,17,18, 20, 24). In the present study, recurrence rate (37%) was higher than that of Kashan-Iran study (24%) which

was a one year follow-up of 50 children with FS and Fisher's exact test was used for statistical analysis of the data. In that study, a positive family history of FS, occurrence of seizure within an hour from the onset of fever and in children younger than one year were risk factors of febrile seizure recurrence(45).

In conclusion, In this study, seizure in children younger than one year old was one of risk factors of febrile seizure recurrence and they had more prolonged seizure. Therefore, febrile seizure must be considered more serious in this age group and recurrent FS must be followed more exactly.

Antipyretic administration was not effective in preventing seizure recurrence but active measures to control fever, including the use of antipyretics, may reduce discomfort and are reassuring.

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