Recurrence of febrile seizure in Yazd, Iran

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Febrile seizure (FS) is the most common problem in pediatric neurology. The purpose of this study was to determine FS recurrence frequency and to evaluate its risk factors. In a descriptive retrospective study, 139 children with first FS, admitted between March 2004 and August 2005 in Yazd Shaheed Sadoughi Hospital, were followed. Seventy-six boys and 63 girls with a mean age of 2.03±1.21 years were followed for 25.1±5.5 months. Thirty-seven percent had FS recurrence, with a mean recurrence time of 6.7±5.9 months. Sixty-five percent of infants and 30% of children >1 year old had FS recurrence. Sixty-three percent of those with seizure occurring in <1 hour of fever duration had FS recurrence, while only 33% of those with seizure after >1 hour of fever duration had FS recurrence. Seizures in children <1 year old and in <1 hour of fever duration were risk factors for FS recurrence.

Key words: febrile seizure, first febrile seizure, febrile seizure recurrence.

Febrile seizure (FS) is the most common type of childhood seizures[1]. It is also a common cause of pediatric admission and parental concern. The incidence varies from 0.35%-1.5% in China[2] to 14% in Guam[3]. A FS is defined by the International League Against Epilepsy as a seizure occurring in association with a febrile illness in the absence of central nervous system (CNS) infections or acute electrolyte imbalance and without prior afebrile seizures in children older than one month[4]. According to Berg[5], FSs are defined as occurring between 6 months and 6 years of age. The child may be neurologically normal or abnormal.

Febrile seizures (FSs) are further classified as simple or complex. A FS is complex if it is focal or focal findings are present during the postictal period, prolonged more than 10-15 minutes, or multiple (occurrence of more than 1 seizure during the febrile illness)[4].

One major concern in dealing with first FS is the risk of recurrence. Risk factors for recurrence after first FS, based on different studies, are:

1. Age less than one year[1-4,6-12]
2. Family history of febrile seizures[1-3,6-9, 11-16]
3. Seizure in temperatures of less than 40°C[1-4,6-8,11,12,14]
4. FS within an hour of recognized onset of fever[1, 2, 6,7]
5. Complex features[1,2,5,6,9,10,16,17] : prolonged[18], multiple[3], focal[11]
6. Family history of epilepsy[2,7-11]
7. Male sex[17]
8. Parental consanguinity[10]
9. Attendance at day care[2,13]
10. Recurrent febrile seizure[19]

Simple FS, especially in a child older than 12 months, is considered as benign disease, which requires neither specific tests [laboratory test, lumbar puncture, neuroimaging (computerized tomography [CT] or magnetic resonance imaging [MRI]), EEG], nor specific treatment[1]. However, complex FS is accompanied with further complications such as: meningitis[1,20], recurrent FS[1,2,4,6,9,10,16,17], subsequent epilepsy[1-3,8,19], and status epilepticus[1].

Preventing or aborting prolonged FSs to prevent status epilepticus with its attendant complications, however, remains a rational goal[19]. Diazepam given orally or rectally at the time of onset of a febrile illness will

reduce the probability of a recurrent FS, and is indicated particularly in children at risk for prolonged or multiple FS and in those who live far from medical care or to allay familial anxiety[1]. Prophylactic daily anticonvulsant should be considered in infants with abnormal neurological exam or developmental delay, complex FS with positive family history of epilepsy, and frequent and prolonged FS[21]. Multiple recurrences of FS predispose the child with FS to subsequent epilepsy[20,22]. The association between FS and epilepsy, however small, may demonstrate a genetic link between FS and epilepsy rather than a cause and effect relationship[23].

Anticonvulsants such as phenobarbital and diazepam have been found to reduce the recurrence of FSs, but not subsequent development of epilepsy[4].

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

Material and Methods

This descriptive retrospective study included 139 children with first FS, admitted between March 2004 and August 2005 in Yazd Shaheed Sadoughi Hospital, and followed for 15-36 months from the point of view of seizure recurrence. We utilized Berg's definition of age range of 6 months - 6 years in FS. Children with history of afebrile seizure, evidence of CNS infection, shigellosis encephalopathy, or electrolyte abnormalities were excluded. Maximum temperature was defined as the highest rectal temperature recorded during the period of admission. The patients' characteristics, i.e., sex and age at presentation of FS, type and duration of seizure, type of FS (simple or complex), family history of febrile/afebrile seizure in first- and second-degree relatives, fever duration, developmental status, and maximum temperature, were reviewed. The developmental status of the patient was assessed by a pediatrician and a pediatric neurologist. The data were 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 recurrence of FS. Risk factors were initially examined by univariate analysis. Rate ratios (RRs) were calculated for individual risk factors with 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 the probability of recurrence during the follow-up period. Statistical significance was taken as $p<0.05$.

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

Results

Seventy-six boys and 63 girls with a mean age of 2.03±1.21 years were followed for 25.1±5.5 months. The male: female ratio was 1.2 : 1. Thirty-three percent (46/139) had complex FS, among whom 23 had multiple convulsions within 24 hours, 9 showed focal features and 14 had prolonged convulsion.

The mean seizure duration was 8±5.6 minutes in infants and 6.7±5.3 minutes in children >1 year old. Seizure was more prolonged in infants ($p=0.04$).

Fifty-two patients had recurrent FS, 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 1 month, 67.3% by 6 months, 88% by 1 year and 94% by 18 months. The recurrence rate displayed no further increasing trend by 2 years after the first episode.

Mean time of recurrence in the different age groups is shown in Table I, which indicates that FS recurrence was later ($p=0.014$) in children >4 years.

Six children had neurodevelopmental delay (NDD), among whom first FS at <1 year of age was seen in 2, while 4 showed FS in 1-2 years. These 4 patients had recurrence of FS. Developmental state of children had not changed at the end of the follow-up.

Of the 52 who recurred, 67% (35/52) had 1, 23% (12/52) had 2, and 10% (5/52) had more than 2 recurrences. Table II shows the number of FS recurrences based on age groups, prophylactic drug usage and developmental status, and indicates that the number of recurrences was higher in the <1 year of age

Table I. Comparison of Mean Recurrence Time According to Age Groups

Age group	Total number	Children with recurrent febrile seizure		Mean recurrence time (mo) ± SD
		Number	Percent	
< 1 years	29	19	65	5.57±4.7
1 – 2 years	63	23	36	6.09±5.4
2 – 4 years	39	10	26	10.7±8.3
> 4 years	8	0	0	0

group (p=0.04). As the method of patient selection was not universal, antiepileptic treatment was prescribed in complicated FS, and a randomized clinical trial should be done in these situations, analysis of data about prophylactic drugs does not seem to be logical.

Univariate analysis of risk factors as shown in Table III indicate that the occurrence of first FS at <1 year of age and FS occurrence in <1 hour of fever duration were risk factors for FS recurrence.

Multivariate analysis disclosed that two factors were statistically significant: early age of onset (<1 year) and seizure in <1 hour of fever duration, which remained significant with Cox regression analysis. The rate ratio (RR) was 1.6 (95% confidence interval [CI] = 1.2 – 2.63 and p value = 0.0001) for early age of onset and 1.7 (95% CI = 1.25 – 2. 92 and p value = 0.02) for fever duration of <1 hour, respectively.

Discussion

The purpose of this study was to determine FS recurrence frequency and to evaluate its risk factors. We used FS definition based on pediatric textbook[24] and Berg[5], who is a master in FS.

One-third of our patients had complex FS, but in other studies, this rate varies between 6.7% and 35%[1,3,5,16,18,24,25]. Possible explanations for this variety are: ethnical and geographic differences, better diagnosis of partial seizures and methods of patient selection.

The recurrence rate of FS in the present study was 37%, similar to some of the other studies[1-3,6,9,19], which varied between 15% and 48%[6,13,14,17]. Possible explanations for this difference are: follow- up duration, ethnical and geographical differences, methods of patient selection, and sample size. In the present study, FS in infants (<1 year) was more prolonged (similar to Farwell's result[25]) and was one of the risk factors for FS recurrence, which is in agreement with other studies[1-4,6,7-12] that state that early age of onset of FS seems to be the most consistent risk factor for FS recurrence. This relation appears to be due to the fact that, in view of the younger age at onset, the child will be in the age group at risk for FS for a longer period[1].

This study showed that the shorter the duration of recognized fever, the higher the chance of recurrence, and seizure occurring in <1 hour of fever duration was a risk factor for FS recurrence, which is in agreement with other studies[1,4,24,26].

Table II. Frequency of Recurrence of Febrile Seizure Based on Some Factors

Factor	Recurrent FS	No	One time	Two times	>2 times	P Value
Age at first seizure	<1 year	10	14	4	1	0.04
	>1 year	77	21	8	4	
Prophylactic drugs	No	62	30	9	3	0.28
	Diazepam in fever	15	0	0	1	
	Continuous phenobarbital	10	5	3	1	
Neurodevelopmental delay	Yes	2	2	2	0	0.224
	No	85	33	10	5	

Table III. Risk Factors for Recurrence of Febrile Seizure Using Univariate Analysis

Factor		Recurrence	No Recurrence	P Value
Age at first seizure	<1 year	19	10	0.0001
	>1 year	33	77	
Type of febrile seizure	Simple	32	61	0.298
	Complex	20	26	
Fever duration	<1 hour	12	7	0.01
	>1 hour	40	80	
Sex	Male	24	52	0.119
	Female	28	35	
Seizure at T <40°C	Yes	51	84	0.6
	No	1	3	
Antipyretic usage in other febrile episode	Yes	34	52	0.5
	No	18	35	
Positive family history of FS in 1st-2nd degree relatives	Yes	13	15	0.27
	No	39	72	
Positive family history of epilepsy in 1st-2nd degree relatives	Yes	10	11	0.294
	No	42	76	
Developmental delay	Yes	4	2	0.13
	No	48	85	
Seizure duration	Yes	8	6	0.269
>10 min	No	44	81	
Seizure type	Generalized	50	80	0.45
	Focal	2	4	
	Secondary generalized	0	3	
EEG results	Normal	18	13	0.46
	Nonspecific abnormal	22	11	
	Epileptic abnormality	3	4	

In this study, 65% of children <1 year old had FS recurrence. This figure is higher than those of other studies (50%)[1,4,24] and lower than reported in another study (73%)[8]. More prolonged seizures in infants may be a possible explanation for the result of our study.

In this study, 13.7% of the children experienced their seizure either before or within 1 hour of onset of fever, which is lower than that of Berg's study (21%)[12]. On the other hand, FS occurred in spite of use of a full dose of antipyretic in 62% of patients, and use or not of antipyretic had no effect on FS recurrence, which supports the results of other studies indicating that prophylactic antipyretic is not recommended to reduce the recurrence rate and was not effective in preventing FS occurrence[23,25].

In the present study, EEG results had no value in predicting recurrence of FS, as in other studies [2,27,28]. The recommendation found in a pediatric neurology textbook that an EEG should be done in children with complex FSs who have a recurrence without fever or in children with recurrent FSs who exhibit developmental delays or neurologic deficits must be considered[1].

In our study, complex FS was not associated with an increased risk of recurrence of FS, which is in accordance with some studies[1,11,12,14] but not in agreement with others[1,2,4,6,9,10,16,17]. Possible explanations for this discrepancy are: the number of patients, patient selection methods and better diagnosis of partial seizures.

In this study, NDD was not a risk factor for recurrent FS, which is in agreement with other studies[1,11,12,18].

In conclusion, in this study, seizure in children <1 year old was one of the risk factors for FS recurrence and they had more prolonged seizures. Therefore, FS must be considered as more serious in this age group.

We showed that infants experiencing FS at the onset of fever have a higher risk of recurrence. This has implications when considering prophylactic strategies that rely on giving medications at the onset of febrile illness[1].

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

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