Afebrile seizure subsequent to initial febrile seizure

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INTRODUCTION Febrile seizure (FS) is the most common paediatric neurological problem. The purpose of this study was to determine the frequency of afebrile seizures subsequent to FS in children with initial FS and to evaluate its risk factors.

METHODS A prospective study was conducted on all children (age 6 months to 6 years) referred with initial FS to the Shahid Sadoughi Hospital, Yazd, Iran, between August 2004 and March 2006, who were followed up for at least 15 months for the occurrence of subsequent afebrile seizures.

RESULTS 161 boys and 120 girls (mean age 2.12 ± 1.33 years) were followed up for 34.1 ± 7.8 months. 87 (31%) patients had complex FS and 19 (6.7%) patients had subsequent afebrile seizure, with a mean occurrence time of 10.6 ± 6.4 months. Univariate analysis using chi-square test showed that initial FS within one hour of developing fever (p = 0.0001), neurodevelopmental delay (p = 0.0001), family history of epilepsy (p = 0.0001), recurrent FS (p = 0.003) and focal FS (p = 0.04) were risk factors for subsequent afebrile seizure. On multivariate analysis, neurodevelopmental delay (odds ratio [OR] 2.6, 95% confidence interval [CI] 2.3–3.4), initial FS within one hour of developing fever (OR 1.7, 95% CI 1.2–2.1) and family history of epilepsy (OR 1.5, 95% CI 1.1–1.9) were significant factors.

CONCLUSION Special attention should be paid to children with FS during history-taking and developmental assessments to identify high-risk patients and those who might need prophylactic anticonvulsants.

Keywords: afebrile seizure, complex febrile seizure, epilepsy
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INTRODUCTION

Febrile seizure (FS) is the most common type of childhood seizures. It is also a common cause of paediatric admission and parental concern. The reported incidence of FS is varied, ranging from 0.35%–1.5% in China[1] to 14% in Guam.[2] FS has been defined by the International League Against Epilepsy as a seizure associated with a febrile illness in the absence of central nervous system (CNS) infections or acute electrolyte abnormalities in a child older than one month without previous afebrile seizures.[3] According to Berg, FS can occur between six months and six years of age.[4] It may also occur in children with normal or abnormal neurological development. FS is further classified as simple or complex, with complex FS defined as seizure lasting more than 15 minutes, repeated seizures occuring within 24 hours and focal seizure activity or focal findings present during the postictal period.[5]

One major concern when dealing with children with initial FS is the risk of subsequent epilepsy; 10%–15% of epileptic patients have a history of FS, which is several times higher than that in the general population (range 2%–4%).[6] The risk factors for subsequent epilepsy after initial FS, based on different studies, are: (1) neurodevelopmental delay and abnormal neurological examination;[1,7-11] (2) complex features[7,9-13] – focal[10,11,13,14] or prolonged;[8,14] (3) family history of epilepsy;[1,7,8,10,15,16] (4) FS at < one year of age;[1,8,15] (5) recurrent FS;[10,11] (6) FS within an hour of recognised onset of fever;[9,17] (7) seizure in temperatures < 39°C;[18] (8) late onset of FS (over three years of age);[15] (9) abnormal electroencephalography (EEG);[8,16] and (10) low Apgar scores at five minutes.[15]

Studies have found various risk factors for epilepsy after FS, with some of the most controversial discussions on epilepsy being associated with mesial temporal sclerosis (MTS) due to prolonged FS and the development of complex partial seizures or temporal lobe epilepsy. Some studies have shown that hippocampal injury evolving to hippocampal atrophy is found in children with focal and prolonged complex FS, but not in those with generalised febrile convulsions.[19-21] However, the interpretation of such observations remains a controversy, as such observations suggest acute injury to the hippocampus during FS even while the possibility of pre-existing lesions leading to susceptibility to injury is not excluded.[20] Indeed, epidemiological studies indicate that FS is not associated with major cases of MTS, just as clinicopathological studies have revealed multiple potential causes of MTS and that subtle migration defects may have a role to play.[6] Such associations may represent an inherent susceptibility in some children who are predisposed to prolonged FS and epilepsy simultaneously. Evidence now indicates that a genetic background is an important causal factor for FS and MTS, and that interactions between genetic and environmental factors may contribute to the association between FS and temporal lobe epilepsy.[20] The overall risk of MTS associated with complex FS is about 3%.[22] According to one study, baseline neurological

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disease and personal or family history of epilepsy were higher in children with febrile status epilepticus (seizure lasting > 30 minutes) than in those with briefer FS.[23]

The present study aimed to determine the frequency of afebrile seizure subsequent to initial FS in children in Yazd, Iran, and evaluate the associated risk factors.

METHODS

A prospective study was conducted on all children (age 6 months–6 years) referred with initial FS to the Shahid Sadoughi Hospital, a tertiary hospital in Yazd, Iran, between August 2004 and March 2006, who were followed up for at least 15 months for the occurrence of subsequent afebrile seizures. The Berg definition of FS (age 6 months–6 years) was followed.[4,24] The study was approved by the ethics committee of the hospital.

At the Department of Paediatrics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, children with initial FS are usually admitted to the emergency department and observed for at least 12 hours prior to being discharged or admitted to the paediatric ward based on their conditions. Children with FS (aged < one year), complex FS, evidence of increased intracranial pressure, severe infection (e.g. pneumonia, urinary tract infection), suspected CNS infections and unreliable parents were admitted to the ward. Children with a history of afebrile seizures, evidence of CNS infection, shigellosis encephalopathy, electrolyte abnormalities, and those who could not be followed up, were excluded from the study. The highest rectal temperature recorded during the hospital stay was defined as the maximum temperature.

Variables such as gender, age, developmental status, duration of fever, maximum temperature, type of FS (simple or complex based on medical records), the presence of family history of FS/afebrile seizure in first- and second-degree relatives (based on history-taking and direct interview of the child's parents), and type and duration of seizure (generalised or partial) were reviewed. For improved diagnosis, the patient's developmental status was assessed using the Denver II Developmental Screening Test by a paediatrician and paediatric neurologist.

Data were analysed using the Statistical Package for the Social Sciences version 15 (SPSS Inc, Chicago, IL, USA). The chi-square test was used to compare qualitative variables between patient groups with and without subsequent afebrile seizure, and mean values were compared using the independent *t*-test. Documented risk factors from previous studies were initially examined by univariate analysis using chi-square test, after which multivariate Cox regression analysis was done to examine the risk of occurrence of individual risk factors recognised on univariate analysis. Rate ratios were calculated for individual risk factors with 95% confidence interval (CI). The Kaplan-Meier method was used to calculate the probability of occurrence of afebrile seizure during the follow-up period. A p-value < 0.05 was considered to be statistically significant.

Table I. Risk factors for subsequent afebrile seizure identified on univariate analysis (n = 281).

Factor	Susbsequent afebrile seizures		p-value
	Yes	No	
Gender			
Male	12	149	0.34
Female	7	113	
Age at first seizure (yr)			
< 1	4	57	0.94
> 1	15	205	
Duration of fever prior to initial seizure (hr)			
< 1	9	31	0.0001
> 1	10	231	
Maximum temperature during hospital stay			
38.5°C–40°C	15	251	0.62
> 40°C	4	11	
Developmental delay			
Yes	9	6	0.0001
No	10	255	
FS type			
Simple	11	183	0.28
Complex	8	79	
Recurrent FS			
Yes	13	91	0.003
No	6	171	
Seizure type			
Generalised	16	249	0.04
Focal	3	13	
Seizure duration > 10 min			
Yes	4	23	0.32
No	15	239	
Family history of FS			
Yes	10	49	0.07
No	9	213	
Family history of epilepsy			
Yes	14	31	0.0001
No	5	231	

RESULTS

A total of 298 children were referred with initial FS to the Department of Paediatrics during the study period. However, 17 patients were lost to follow-up and excluded. 161 boys and 120 girls (mean age 2.12 ± 1.33 years) met the criterion of follow-up for at least 15 months. The mean duration of follow-up was 34.1 ± 7.8 (range 15–48) months. 194 (69%) patients presented with simple FS and 87 (31%) children had complex FS. Among those with complex FS, 44 children had multiple seizures within 24 hours, 16 had focal features and 27 had prolonged convulsions.

The age-wise distribution of children with initial FS indicated that a majority were 1–2 years of age: < 1 year (n = 61); 1–2 years (n = 124); 2–4 years (n = 81): and > 4 years (n = 15). The most common aetiologies of fever were upper respiratory tract infection (n = 93, 33%), gastroenteritis (n = 57, 20.3%), otitis media (n = 53, 18.9%) and unknown causes (n = 45, 16%). 14 patients had neurodevelopmental delay, the aetiologies for which were

structural CNS dysgenesis (n = 6), asphyxia (n = 5), neonatal intracranial haemorrhage (n = 2) and neonatal sepsis (n = 1). 19 (6.7%) patients had subsequent afebrile seizures (tonic-clonic generalised seizure n = 12; tonic seizure n = 4; clonic seizure n = 2; atonic seizure n = 1), with a mean occurrence time of 10.6 ± 6.4 months. The cumulative percentage of afebrile seizure occurrence, according to the Kaplan-Meier method, was 31% at one month, 78% at six months, 87% at one year and 92% at 18 months. During follow-up, the occurrence rate did not show any further increase at two years after the first episode. Three children had status epilepticus, but none of them had subsequent afebrile seizures. Partial seizure was not seen in any patient. Five patients had a history of birth asphyxia and one had closed lip schizencephaly. The aetiologies of subsequent afebrile seizures were not found for 13 children.

Univariate analysis of risk factors (Table I) indicated that initial FS within one hour of developing fever (p = 0.0001), neurodevelopmental delay (p = 0.0001), positive family history of epilepsy in first- and second-degree relatives (p = 0.0001), recurrent FS (p = 0.003) and focal FS (p = 0.04) were risk factors for afebrile seizures subsequent to initial FS. Multivariate analysis revealed statistical significance for only three of the above factors – neurodevelopmental delay, family history and seizure within one hour of developing fever. Multivariate Cox regression analysis revealed the risk of occurrence of these factors as: neurodevelopmental delay (odds risk [OR] 2.6, 95% CI 2.0–3.4 p = 0.0001); initial FS within one hour of developing fever (OR 1.7, 95% CI 1.2–2.1 p = 0.02); and positive family history of epilepsy (OR 1.5, 95% CI 1.1–1.9 p = 0.03).

DISCUSSION

The majority of patients in this study were boys (57%), and the occurrence of initial FS was also more common in boys, similar to other reports,[1,15] although the frequency of subsequent afebrile seizures was not statistically different between the genders. Complex FS was seen in 31% of patients in this study, although other studies have reported a range of prevalence (6.7%–35%).[2,4,19] This difference in findings may be due to a variety of reasons, including ethnic and geographic differences, better diagnosis of partial seizures and improved methods of patient selection. Subsequent afebrile seizures were seen among 6.7% of patients in the present study, which was similar to some reports[7,15] but different from others (range 0.9%–12%).[1,2,9-11] The disparity in findings may be attributable to various factors such as the age of children enrolled, type of FS, period of follow-up and sample size, in addition to ethnic and geographical differences and methods of patient selection.

Studies have established the direct relationship between the number of risk factors and the rate of subsequent afebrile seizures.[7,9] Fetveit found that the most important risk factors for subsequent afebrile seizures were the presence of developmental or neurological abnormality, family history of epilepsy and complex FS.[7] Sadleir and Scheffer found that prolonged FS was associated with an increased incidence of epilepsy (21%), with the risk rising to 49% for children with all three features of complex FS.[9]

We found that seizure within an hour of the recognised onset of fever was a risk factor for subsequent afebrile seizures, similar to some earlier studies,[9,17] as was family history of epilepsy, which is also in agreement with other reports.[1,7,8,10,11,15,16] These findings support the suggestion that the association between FS and epilepsy may demonstrate a genetic link between FS and epilepsy rather than a cause and effect relationship.[7] Neurodevelopmental delay was also a significant risk factor for subsequent afebrile seizure, similar to other reports.[1,7-11] In view of these findings, the general recommendation of EEG for a child with FS and neurodevelopmental delay or neurological deficits seems to be well supported.[1,6,25] It should be noted that a majority of children would have minor electroencephalographic abnormalities[7,8] if the EEG is done within the first month after FS and that definite paroxysmal epileptic discharges (spikes, spike and wave, and poly spike and wave discharges) in EEG are highly suggestive of subsequent epilepsy in a child.[8]

The determination of risk factors for subsequent afebrile seizures following initial FS in children is not only important for the timely recognition of susceptible children but also has clinical implications, as such children may need special attention.[11,15] Studies have reported various risk factors for epilepsy after initial FS. We found that subsequent afebrile seizures did not occur in a majority of children with FS. However, neurodevelopmental delay, initial FS within one hour of developing fever and family history of epilepsy were risk factors for subsequent afebrile seizures in children. Special attention should be paid to children with FS during history-taking and developmental assessments to identify high-risk patients and those who may need prophylactic anticonvulsants. Studies with longer follow-up periods and larger sample sizes are needed to further corroborate the results of this study.

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REFERENCES

1. Leung AK, Robson WL. Febrile seizures. J Pediatr Health Care 2007; 2:250-5.
2. Waruiru C, Appleton R. Febrile convultions: an update. Arch Dis Child 2004; 89:751-6.
3. Jones T, Jacobsen SJ. Childhood febrile seizures: overview and implications. Int J Med Sci 2007; 4:110-4.
4. Berg AT. Are febrile seizures provoked by a rapid rise in temperature? Am J Dis Child 1993; 147:1101-3.
5. Johnson MV. Febrile Seizure. In: Behrman RE, Kliegman RM, Jenson HB, Stanton BF, eds. Nelson Textbook of Pediatrics, 18th ed. Philadelphia: Saunders; 2007: 2457-80.
6. Shinnar S. Febrile Seizures. In: Swaiman KF, Ashwal S, Ferriero DM, eds. Pediatric Neurology: Principles and Practice, 4th ed. Philadelphia: Mosby Elsevier; 2007: 1079-89.
7. Fetveit A. Assessment of febrile seizures in children. Eur J Pediatr 2008; 167:17-27.

8. Varma RR. Febrile seizures. Indian J Pediatr 2002; 69:697-700.
9. Sadleir LG, Scheffer IE. Febrile seizures. BMJ 2007; 334:307-11.
10. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med 1976; 295:1029-33.
11. Tsai ML, Hung KL. Risk factors for subsequent epilepsy after febrile seizures. J Formos Med Assoc 1995; 94:327-31.
12. Durá-Travé T, Yoldi-Petri ME. [A long-term follow-up of 234 children with febrile seizures]. Rev Neurol 2004; 39:1104-8. Spanish.
13. Sapir D, Leitner Y, Harel S, Kramer U. Unprovoked seizures after complex febrile seizures. Brain Dev 2000; 22:484-6.
14. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile seizures. N Engl J Med 1987; 316:493-8.
15. Vestergaard M, Pedersen CB, Sidenius P, Olsen J, Christensen J. The long-term risk of epilepsy after febrile seizures in susceptible subgroups. Am J Epidemiol 2007; 165:911-8.
16. Birca A, Guy N, Fortier I, et al. Genetic influence on the clinical characteristics and outcome of febrile seizures--a retrospective study. Eur J Paediatr Neurol 2005; 9:339-45.
17. Berg AT, Shinnar S. Unprovoked seizures in children with febrile seizures: short term outcome. Neurology 1996; 47:562-8.
18. El-Radhi AS. Lower degree of fever at the initial febrile convulsion is associated with increased risk of subsequent seizures. Eur J Paediatr Neurol 1998; 2:91-6.
19. Barr WB, Ashtari M, Schaul N. Bilateral reductions in hippocampal volume in adults with epilepsy and a history of febrile seizures. J Neurol Neurosurg Psychiatry 1997; 63:461-7.
20. Cendes F. Febrile seizures and mesial temporal sclerosis. Curr Opin Neurol 2004; 17:161-4.
21. Scott RC, King MD, Gadian DG, Neville BG, Connelly A. Prolonged febrile seizures are associated with hippocampal vasogenic edema and developmental changes. Epilepsia 2006; 47:1493-8.
22. Chungath M, Shorvon S. The mortality and morbidity of febrile seizures. Nat Clin Pract Neurol 2008; 4:610-21.
23. Shinnar S, Pellock JM, Berg AT, et al. Short-term outcomes of children with febrile status epilepticus. Epilepsia 2001; 42:47-53.
24. Lewis D. Paroxysmal Disorders. In: Kliegman RM, Marcdnate KJ, Jenson HB, Behrman RE, eds. Nelson Essential of Pediatrics, 5th ed. Philadelphia: Saunders; 2006: 833-40.
25. Cuestas E. Is routine EEG helpful in the management of complex febrile seizures? Arch Dis Child 2004; 89:290.

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