

Prognostic factors for epilepsy following first febrile seizure in Saudi children

Abdullah I. Almojali,^a Anwar E. Ahmed,^b Muhammed Y. Bagha^c

From the ^aCollege of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; ^bDepartment of Epidemiology and Biostatistics, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; ^cDepartment of General Pediatrics, King Abdulaziz Medical City, Riyadh, Saudi Arabia

Correspondence: Dr. Abdullah Ibrahim Almojali · College of Medicine, King Saud bin Abdulaziz University for Health Sciences, PO Box 22490, Riyadh 11426, Saudi Arabia · T: +966-11-4299999 · AbdullahAlmojali@gmail.com · <http://orcid.org/0000-0003-4208-4196>

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BACKGROUND: Febrile seizure is the most common convulsive event during childhood, but it is generally considered benign.

OBJECTIVES: To estimate the rate of epilepsy after first presentation of febrile seizure and to describe factors that can predispose children to have subsequent epilepsy after their first febrile seizure.

DESIGN: Retrospective chart review.

SETTING: A tertiary care center in Riyadh.

PATIENTS AND METHODS: All children whose first febrile seizure developed between 2009–2012, and who were admitted to the pediatric wards.

MAIN OUTCOME MEASURES: The rate of epilepsy and prognostic factors for epilepsy following first febrile seizure.

RESULTS: Of 109 febrile seizure patients, 6 (5.5%, 95% CI: 2.1% - 11.6%) were diagnosed with subsequent epilepsy 5 to 46 months after their first febrile seizure. The risk of having subsequent epilepsy was higher in children who were convulsing at a low-grade fever during their first febrile convulsion ($P=.02$). Moreover, delayed vaccination status ($P=.03$), prolonged duration of the first convulsion ($P=.04$), frequent febrile seizures ($P=.01$), and fever without documented infection ($P=.03$) during the first febrile convulsion were associated with epilepsy.

CONCLUSION: The rate of epilepsy following first febrile seizure in Saudi children is within the range of values reported in different populations. Although most childhood febrile seizures are self-limiting, careful observation is needed, particularly for children who exhibit factors associated with epilepsy.

LIMITATIONS: Conducted at a single center in Saudi Arabia, which may limit generalizability.

Febrile seizure is considered the most common convulsive event of childhood, occurring in 2% to 5% in infants and children. The American Academy of Pediatrics (AAP) defines febrile seizures as seizures accompanied by fever ($>38^{\circ}$ by any method) that occur in neurologically healthy infants and children (6 through 60 months of age) who do not have intracranial infection, metabolic disturbance, or a history of afebrile seizures.¹ They are sub-classified into two categories: simple and complex. Simple febrile seizure is generalized, lasting less than 15 minutes and occurs once in a 24-hour period, whereas complex febrile seizures are seizures that have one or more of the following features: prolonged duration of more than 15

minutes, focal features, or recurrence within 24 hours of the first episode.²

On the other hand, epilepsy is defined as the occurrence of two episodes or more of unprovoked, afebrile seizures in two different days.^{3,4} It has been reported that approximately 10% to 15% of epileptic children have previously had febrile seizures.^{5,6} However, a systematic review of 33 studies (between January 1993 and June 2007) that addressed the risk of epilepsy after febrile seizures found that only 16 studies (out of 33 papers) reported the risk of subsequent epilepsy after a febrile seizure, which lies between 2.0% and 7.5%.⁷ Locally, in Saudi Arabia, the rate of developing epilepsy after a febrile seizure has not been investigated.

However, one retrospective study of 341 patients with epilepsy in a regional hospital in Al-Qassim reported that only a few patients of those who had history of febrile seizures.⁸

Although febrile seizures are generally considered benign and self-limiting, there is much debate about and conflict in the risk of developing epilepsy in children with history of febrile seizures.⁹ Additionally, when parents witness their child's convulsion for the first time, they understandably become anxious and afraid.^{10,11} Uncertainty and lack of information about febrile convulsions and their serious complications like epilepsy and death were reported as common contributors of parents' anxiety.^{11,12} Therefore, to obtain a more comprehensive picture, this retrospective study aimed to estimate the rate of development epilepsy after first presentation of febrile seizure in a tertiary health care hospital in Saudi Arabia and to describe the factors that can predispose children to have subsequent epilepsy after their first febrile seizure.

PATIENTS AND METHODS

This retrospective chart review was conducted in the pediatric section at King Abdulaziz Medical City (KAMC), which is one of the largest tertiary hospitals in Riyadh, Saudi Arabia. The pediatric section at KAMC is composed of different pediatric subspecialties units, including general pediatric, surgical, cardiac, intensive care and pediatrics emergency units.

All children who had their first febrile seizure between January 2009 and December 2012, and were admitted to the pediatric department of King Abdulaziz Medical City in Riyadh were included in the study. The definition of American Academy of Pediatrics of febrile seizures was followed and used as inclusion/exclusion criteria.¹ Epilepsy was defined as the occurrence of at least two episodes of afebrile seizures on two different days.^{3,4} According to the patient records, the diagnosis of epilepsy was made based on the definition, accounts of the episodes, clinical course or investigations (EEG and neuroimaging studies). The median follow-up period was 72 months (range, 48 months - 84 months).

The study was conducted in adherence with ethical policies. It was approved by the Institutional Review Board of King Abdullah International Medical Research Center (KAIMRC) (IRBC/695/16). The anonymity and confidentiality of the research subjects and their medical records was maintained. The data obtained from their records included demographic data, clinical presentation of first febrile seizure type (age at presentation, body temperature, underlying causes of fever, number of seizures during the day, duration and type

of convulsion), developmental, past medical and family history. Complete blood count, electrolyte levels and lumbar puncture results, if available, were checked to exclude any child with pre-existing neurodevelopmental disorders, brain injury, evidence of central nervous system infection, electrolyte abnormalities, or history of afebrile seizures before the first febrile seizure.

Data were entered in Microsoft Excel and analyzed using IBM SPSS version 22. The rate of subsequent epilepsy was reported as percent with 95% CI. Categorical variables were presented by frequency and percentages, and continuous variables by mean and standard deviation. The effect of demographics and clinical presentation of first febrile seizures on developing later epilepsy was assessed by the Fisher Exact Test or Linear-by-Linear Association for categorical values, and the *t* test for continuous values. A *P* value of less than .05 was considered as statistically significant.

RESULTS

The total number of children who had their first febrile seizure during the period January 2009–December 2012, and were admitted to the pediatric department of KAMC was 149. Of the 149 children, forty were excluded because of a history of afebrile seizure (*n*=9), developmental delay (*n*=9), intracranial infection or brain injury (*n*=7), acute electrolyte imbalances (*n*=4), or age was <6 months or >5 years (*n*=11). Therefore, 109 children were included in this study.

Of the 109 children, there were 58 boys (53.2%) and 51 girls (46.8%). Their median age at presentation of first febrile seizure was 15 months (range, 5-58 months). Prematurity (range, 34-36 weeks) was reported in 12 children (11%), and consanguinity of parents was reported in 39 cases (35.8%). First febrile seizure was simple in 47.7% of the children (*n*=52) and complex in 52.3% (*n*=57). Infection was the most common cause of fever (75.2%, *n*=82), especially respiratory tract infection (45.8%, *n*=50) followed by acute gastroenteritis (20.2%, *n*=22). Fever (without a documented infection/cause was reported in 24.8% (*n*=27). Demographic and clinical characteristics of the children and their first febrile seizure are shown in **Table 1**.

Among the 109 children in this study, six (5.5%, 95 CI: 2.1%-11.6%) were diagnosed with subsequent epilepsy after 5-46 months from their first febrile seizure. Comparison between the febrile seizures-only group (*n*=103) and the subsequent epilepsy group (*n*=6) in terms of their baseline characteristics is shown in **Table 2**, and in terms of the clinical presentation of their first febrile seizures in **Table 3**. Children who had a low-grade fever (38.0 to 39.0°C, measured by tympanic

Table 1. Demographic and clinical characteristics of the study subjects and their first febrile seizure (N=109).

Characteristics	Levels	n	%
Gender	Male	58	53.2
	Female	51	46.8
Birth order	<4	58	53.2
	≥4	51	46.8
Gestation	Preterm birth	12	11.0
	Full-term birth	97	89.0
Vaccination status	Up-to-date	94	86.2
	Delayed	15	13.8
Consanguinity of the parents	Yes	39	35.8
	No	70	64.2
Family history of epilepsy	Yes	15	13.8
	No	94	86.2
Type of 1st febrile convulsion	Generalized	98	89.9
	Focal	11	10.1
Duration of 1st febrile convulsion	<1 minute	44	40.4
	1-15 minutes	48	44.0
	>15 minutes	17	15.6
Recurrence in first 24 hours	Yes	40	36.7
	No	69	63.3
Type of 1st febrile seizure	Simple	52	47.7
	Complex	57	52.3
The source of the febrile illness	Unknown	27	24.8
	RTI	50	45.8
	AGE	22	20.2
	Others	10	9.2

RTI, Respiratory Tract Infection; AGE, Acute Gastroenteritis.

Table 2. Baseline characteristics of children with only one febrile seizure (n=103) and children with a subsequent seizure (n=6).

Characteristics	Level	Febrile seizure only (n=103)	Subsequent Epilepsy (n=6)	P value
Gender	Male	53 (51.5)	5 (83.3)	.21
	Female	50 (48.5)	1 (16.7)	
Birth order	< 4	56 (54.4)	2 (33.3)	.41
	≥ 4	47 (45.6)	4 (66.7)	
Gestation	Preterm birth	10 (9.7)	2 (33.3)	.11
	Full-term birth	93 (90.3)	4 (66.7)	
Vaccination status	Up-to-date	91 (88.3)	3 (50.0)	.03
	Delayed	12 (11.7)	3 (50.0)	
Consanguinity of the parents	Yes	37 (35.9)	2 (33.3)	.99
	No	66 (64.1)	4 (66.7)	
Family history of epilepsy	Yes	14 (13.6)	1 (16.7)	.99
	No	89 (86.4)	5 (83.3)	

Values are presented as number (%).

P values were calculated using the Fisher Exact Test.

Statistically significant values are bolded.

route) during their first febrile convulsion were more likely to develop subsequent epilepsy ($P=.02$). The mean (SD) body temperature in the subsequent epilepsy group was 38.4 (0.4)°C, while it was 39.2 (0.8)°C in children who did not develop epilepsy. Delayed vaccination status ($P=.03$), prolonged duration of the first convulsion ($P=0.04$), multiple febrile seizures ($P=.01$), and fever without documented infection ($P=.03$) during the first febrile convulsion were associated with epilepsy.

DISCUSSION

The present study revealed that the rate of developing subsequent epilepsy in children after their first febrile seizure was 5.5% (95 CI: 2.05%-11.60%), which is almost five times that of the general population risk of epilepsy (1.2% by age 24).¹³ This is similar to the results of several studies, which found that the risk of developing epilepsy following febrile seizures was 6%.¹⁴⁻¹⁷ Many studies document that the risk of developing epilepsy following simple febrile seizure is similar to the general population risk, while it increases by several folds in case of complex febrile seizures.^{2,15,16,18} However, in our study, the only feature among the features of the

Table 3. Association between febrile convulsion's patients and those who developed subsequent epilepsy in terms of the clinical presentation of their first febrile seizure.

Characteristics	Level	Febrile seizure only (n=103)	Subsequent Epilepsy (n=6)	P value
Age at presentation (by months)		18.7 (11.4)	12.3 (6.7)	.18
Peak temperature (by Celsius)		39.2 (0.8)	38.4 (0.4)	.02
Type of convulsion	Generalized	94 (91.3)	4 (66.7)	.11
	Focal	9 (8.7)	2 (33.3)	
Duration of convulsion	<1 minute	43 (41.7)	1 (16.7)	.04
	1-15 minutes	46 (44.7)	2 (33.3)	
	>15 minutes	14 (13.6)	3 (50.0)	
Recurrence in first 24 hours	Yes	39 (37.9)	1 (16.7)	.41
	No	64 (62.1)	5 (83.3)	
Number of total seizures		1.2 (1.4)	2.7 (1.8)	.01
Type of febrile seizure	Simple	50 (48.5)	2 (33.3)	.68
	Complex	53 (51.5)	4 (66.7)	
The source of the febrile illness	Unknown	23 (22.3)	4 (66.7)	.03
	Infection	80 (77.7)	2 (33.3)	

Values are presented as mean (standard deviation) or number (%).

P values were calculated using the Fisher's Exact Test or Linear-by-Linear Association for categorical values, and t test for continuous values.

Statistically significant values are bolded.

three complex febrile seizures that was associated with later epilepsy was a prolonged duration of more than 15 minutes.

As reported in a recent systematic review, the main problem with the majority of such studies is the lack of clarity in categorizing seizures as complex versus simple and not excluding children who have neurological or developmental disabilities.¹⁹ In the present study, any child with pre-existing neurodevelopmental disorders or brain injury was excluded, since these abnormalities are significant cofounders. This might be a possible explanation for the lack of statistically significant association between the features of the other two complex febrile seizures (focal onset and recurrence within 24 hours) with the development of subsequent epilepsy.

An interesting finding of the present study is that children who were convulsing at a low-grade fever (38.0°C-39.0°C) during their first episode of febrile seizure were more prone to have epilepsy in the future. Although some studies reported that peak temperature during febrile seizures had no relationship with subse-

quent epilepsy,^{16,20,21} a population-based and another hospital-based retrospective study have shown similar findings to ours, where children whose body temperature was <39.0°C during the first FS were more likely to develop subsequent seizures and epilepsy.^{22,23} Of note, although the most common source of fever in the present study was infection, children who had fever without a documented infection or known etiology during their first febrile seizure were more likely to have later epilepsy. It is suggested, as a possible explanation, that each child may have his own temperature threshold for eliciting a febrile convulsion; the lower this threshold is, the more likely are subsequent convulsions and epilepsy.

Additionally, although it is well documented that certain types of vaccines (e.g. measles-mumps-rubella vaccine) independently increase the risk of developing febrile seizures,^{24,25} the present study shows that the rate of subsequent epilepsy after the first episode of febrile seizure increased in children who missed their scheduled vaccines. To the best of our knowledge, no previous studies have examined the association of a child's

immunization status during the first presentation of febrile convulsion with the development of subsequent epilepsy. However, Dr Sun et al found that children who were vaccinated by diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and *Haemophilis influenzae* Type b (DTaP-IPV-Hib) vaccine had a lower risk of epilepsy in the first 15 months of life compared to unvaccinated children.²⁵ Unfortunately, we had insufficient details about the type of missed vaccinations. Further studies are needed to investigate the influence of each vaccine and its association with epilepsy.

In this study, gender, prematurity, consanguinity and family history of epilepsy show no association with the risk of later epilepsy in children with febrile seizures. There was a trend towards having subsequent epilepsy in those who had their first febrile seizure early in life (<1-year-old) but no statistically significant association. However, several studies have reported that the onset of febrile seizures at an early age, prematurity and a family history of epilepsy are among the risk factors for subsequent unprovoked seizures following febrile seizures.^{16,18,21,22} These differences might be due to the different inclusion and exclusion criteria of the studies especially in terms of exclusion or inclusion of children who have genetic or neurodevelopmental abnormalities.

In addition to the retrospective design of this study, the study has other limitations including the small number of patients, especially in the epilepsy group, which

prevented us from running multivariate analysis. Also, some children have only been followed up for just over 4 years, which may underestimate the number of children with subsequent epilepsy or recurrent febrile convulsions. In addition, there can be a considerable bias in the decision to admit a child to the hospital after his first febrile seizure. Moreover, this study was conducted at a single center in Saudi Arabia, which may limit its generalizability. However, further prospective studies using larger populations from multiple centers in Saudi Arabia are recommended to confirm the prognostic factors.

In conclusion, the rate of subsequent epilepsy following the first febrile seizure in a tertiary care hospital in Saudi Arabia is within the range of the values reported in most other communities. Although most childhood febrile seizures are benign and self-limiting, multiple factors have been identified in the present study to be associated with the development of subsequent epilepsy. The child's first febrile seizure that was prolonged in duration, occurred at a low-grade fever, or fever without a documented infection or etiology, was associated with epilepsy. Further studies are needed to confirm those prognostic factors and to investigate the risk of epilepsy in unvaccinated children.

Conflict of interest

None.

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