Seizure 53 (2017) 62–65

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Full Length Article

The risk of subsequent epilepsy in children with febrile seizure after 5 years of age

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ARTICLE INFO

Article history:
Received 9 April 2016
Received in revised form 4 October 2017
Accepted 6 November 2017
Available online xxx

Keywords:
Febrile seizure
Late onset
Epilepsy
Risk factors

ABSTRACT

Purpose: Despite their age-dependent definition, febrile seizures (FS) may be observed in people of almost any age. The risk of developing unprovoked seizures after an FS is well defined. However, there are limited data about FS starting or persisting after 5 years of age. In the present study, we evaluated patients who developed FS after 5 years of age.
Method: Between 2010 and 2014, we prospectively enrolled all patients with FS. We collected demographic and clinical features, radiologic images, electroencephalograms (EEGs), and results of psychomotor development tests and treatment data of the patients. The patients were grouped into two groups. Group 1 consisted of patients who had the first FS after 5 years of age, and group 2 consisted of patients in whom FS persisted after 5 years of age. Fisher's exact test and Pearson's chi-square test were used to analyse the study data and derive conclusions.
Results: Sixty-four patients were enrolled, and afebrile seizure was observed in 12 (18.8%) of them. Nine (14%) patients were diagnosed to have epilepsy in their follow-up examination. Subsequent epilepsy occurrence was independent of gender, mean age, medical history of the patient, family history of epilepsy, presence of afebrile seizure, type of seizure, type of FS, duration of seizure, semiology of seizure, peak fever and EEG and magnetic resonance imaging (MRI) findings in our total cohort. There were no statistical differences between the groups with regard to the occurrence of subsequent afebrile seizure or epilepsy ($p > 0.5$).
Conclusion: Close follow-up is important in patients with FS after the age of 5 years. These seizures are generally benign, but tend to recur and increase the risk of development of epilepsy in the patient. Further studies with a larger cohort are warranted to clarify risk factors and incidence of epilepsy in these patients.

1. Introduction

Febrile seizure (FS) is the most common convulsive disorder in children, and it is defined as a seizure accompanied with fever and without central nervous system infection, which occurs in infants and children of age 6 through 60 months [1]. In 50% of children, the first attack of FS occurs in the second year of life, and in 90% of children, before the age of 3 years [2]. Despite this age-dependent definition, FS may be observed in people of almost any age.

The risk of developing unprovoked seizures after an FS is estimated to be 2% to 5% [3]. The predictive risk factors for the development of epilepsy are developmental delay or an abnormal neurologic examination finding before the onset of the FS, a history of complex FS (including febrile status epilepticus), a first-degree relative with epilepsy and prolonged FS [4]. There are insufficient data about risk factors for epilepsy in children with FS occurring or persistent after 5 years of age.

The aim of our study is to identify the features and predisposing factors for the development of afebrile seizures in children with FS after 5 years of age.

2. Materials and methods

Between 2010 and 2014, we prospectively enrolled all patients with FS that occurred after 5 years of age. We excluded two patients and then grouped the remaining patients into two groups: group 1 consisted of patients who had their first FS after 5 years of

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https://doi.org/10.1016/j.seizure.2017.11.005
1059-1311/

age, and group 2 consisted of patients in whom FS persisted after 5 years of age. An FS was defined in accordance with the definition given by the American Academy of Paediatrics [1]. The demographic (age, gender, background and family history of FS and epilepsy) and clinical features (degree of fever, duration, semiology and frequency of seizures), magnetic resonance imaging (MRI) findings, electroencephalography (EEG) findings, psychomotor development test results and treatment data were evaluated and compared between the two groups. Exclusion criteria were the presence of a history of afebrile seizure, having symptomatic seizures, pathological neurologic background and progressive central nervous system illness. Prophylaxis was given to patients with more than four FS episodes and with abnormal EEG findings.

Definitions: An FS that occurred after 5 years of age was defined as late-onset FS. Persistent FS was defined as FS that occurred both before and after 5 years of age. Complex FS was defined as either focal or multiple seizures, seizures longer than 15 min or a combination of these. Simple FS was defined as a single generalised seizure within 24 h and seizures shorter than 15 min. MRI finding such as white matter lesions or hippocampal malrotations was defined as abnormal. Peak fever was categorised into a low fever group ($<39\,^{\circ}C$) and a high fever group ($\geq 39\,^{\circ}C$). Abnormal EEG was defined as any abnormality on background activity or any epileptiform discharges.

This study was approved by the Local Ethics Committee at the Medical School of Akdeniz University. Informed consent was received from parents or guardians of the children before participation in the study.

Descriptive statistics such as frequency, percentage, mean, standard deviations median and minimum and maximum values were used. For between-group analysis, the Mann-Whitney *U* test was used to analyse the differences between measurements such as the total number of seizures and the mean age, and the chi-square test was used for the duration of seizures, parameters of EEG, MRI, type of seizure, type of FS, family history of FS, family history of epilepsy, consanguinity, WISC-R evaluation, history of prophylaxis, semiology of seizure, presence of afebrile seizure, prenatal history, epilepsy and gender. Risk factors for the development of afebrile seizure were evaluated in univariate analysis, and p values of less than 0.05 were considered to be statistically significant.

3. Results

Among 66 patients in our records, 1 patient with cortical dysplasia and 1 patient who had epileptic encephalopathy that developed during follow-up were excluded from the study. Consequently, 64 patients (26 females and 38 males) were enrolled in the study. The mean follow-up period of the patients was 1 to 3.5 years. The demographic and clinical features are shown in Table 1.

Afebrile seizure was seen in 12 (18.8%) patients. Nine (14%) patients were diagnosed with epilepsy during the follow-up period.

3.1. Evaluation of patients with late-onset FS (group 1, n = 41)

Group 1 consisted of 19 (46%) females and 22 (54%) males, with a mean age of 8.64 ± 2.76 years. Two (5%) patients had a prenatal history of maternal smoking, and 2 (5%) patients were delivered prematurely. One patient was vaccinated with diphtheria and tetanus before the development of seizure. The parents of 8 patients (20%) had consanguinity. Among the mothers of these patients, 27 mothers graduated from primary school, 12 graduated from high school and 2 graduated from college. Among the fathers of these patients, 22 fathers graduated from primary school, 13 graduated from high school and 6 fathers graduated from college. Eight (20%) patients had a family history of FS. Seven (17%) patients had a family history of epilepsy in first-degree relatives. Thirty (73%) patients had a peak fever temperature of up to 39 °C, whereas

Table 1
Comparison of demographic and clinical features of patients.

Demographic Features	Group 1 (n = 41)	Group 2 (n = 23)	P Values	Clinical Features	Group 1 (n = 41)	Group 2 (n = 23)	P Values
Mean age (years ± SD)	8.64 ± 2.76	8.19 ± 2.13	>0.05	Type of Seizure			>0.05
Gender			>0.05	Generalised	36 (88%)	23 (100%)	
Female	19 (46%)	7 (30%)		Focal	3 (7%)	0	
Male	22 (54%)	16 (70%)		Secondary generalised	2 (5%)	0	
Prenatal History			>0.05	Semiology of Seizure			>0.05
Yes	2 (5%)	2 (9%)		Tonic	8 (20%)	3 (13%)	
No	39 (95%)	21 (91%)		Clonic	2 (5%)	0	
Premature delivery	2 (5%)	2 (9%)	>0.05	Tonic-clonic	29 (71%)	19 (83%)	
History of vaccination			>0.05	Atonic	1 (2%)	1 (4%)	
Yes	1 (2%)	1 (4%)		Dialeptic	1 (2%)	0	
No	40 (98%)	22 (96%)		Type of FS			>0.05
Consanguinity			>0.05	Simple FS	29 (71%)	21 (91%)	
Yes	8 (20%)	5 (22%)		Complex FS	12 (29%)	2 (9%)	
No	33 (80%)	18 (78%)		EEG Findings			>0.05
Family history of FS	8 (20%)	12 (52%)	<0.05	Normal	26 (63%)	15 (65%)	
Family history of epilepsy	7 (17%)	5 (22%)	>0.05	Abnormal	6 (15%)	4 (17%)	
Presence of afebrile seizures			>0.05	MRI findings			>0.05
Yes	7 (17%)	5 (22%)		Normal	28 (68%)	17 (74%)	
No	34 (83%)	18 (78%)		Abnormal	2 (5%)	1 (4%)	
Total number of seizures	1.80 ± 1.73	4.52 ± 2.52	<0.05	WISC-R evaluation			>0.05
Peak fever				Normal	14 (34%)	7 (30%)	
37–38 °C	9 (22%)	4 (17%)	>0.05	Abnormal	8 (20%)	5 (22%)	
38–39 °C	21 (51%)	10 (44%)		Prophylaxis			*<0.05*
39–40 °C	10 (25%)	9 (39%)		Yes	10 (24%)	14 (61%)	
>40 °C	1 (2%)	0		No	31 (76%)	9 (39%)	
Duration of seizure			>0.05	Epilepsy			>0.05
>15 min	4 (10%)	2 (9%)		Yes	5 (12%)	4 (17%)	
<15 min	37 (90%)	21 (91%)		No	36 (88%)	19 (83%)	

FS: febrile seizure, EEG: electroencephalography, MRI: magnetic resonance imaging, WISC-R: Wechsler Intelligence Scale for Children, Revised.