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The occurrence of subsequent epilepsy in children with febrile seizures after the age of 5 years old: The truth and theory

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ABSTRACT

Febrile seizures (FS) are age dependent but they can occur almost at any age. The possibility of getting unprovoked seizures after a febrile seizure is well recognized. Although, there are minimal data about febrile seizure starting or persisting after the age of 5 years. The aim of this study is to study the occurrence of febrile seizure after 5 years of age. Materials and Methods: We collected demographic and clinical features, radiologic images, electroencephalograms (EEGs), and results of psychomotor development tests of the patients with febrile seizures attending at The Pediatric Neurology Unit, El-Demerdash Hospital, Ain Shams University, Faculty of Medicine , Cairo; Egypt, prospectively in the period between 2011 and 2015. The patients were grouped into two groups. Group 1 consisted of patients who had the first febrile seizure after 5 years of age, and group 2 consisted of patients in whom febrile seizure persisted after 5 years of age. Statistical analysis: Fisher's exact test and Pearson's chi-square test were used to analyze the study data and derive conclusions. Results: In this study, 50 patients were enrolled, afebrile seizure was observed in 10 (20%) of them and 45 patients (90%) patients were diagnosed to have epilepsy in their follow-up examination. Subsequent epilepsy occurrence was not related to gender, mean age, family history of epilepsy, presence of afebrile seizure, type of seizure, type of febrile seizure, duration of seizure, semiology of seizure, peak fever and EEG and magnetic resonance imaging (MRI) findings in our total cohort. Conclusion: Febrile seizures after 5 years of age are generally benign, but may recur and increase the risk of development of epilepsy in those patients. So, Close follow-up is important and further studies with a larger cohort are needed to clarify predisposing factors and occurrence of epilepsy in those patients.

Key words: Febrile seizure, Child health, late onset, Epilepsy.

Introduction

Seizures are symptoms of a brain problem. They happen because of sudden, abnormal electrical activity in the brain. When people think of seizures, they often think of convulsions in which a person's body shakes rapidly and uncontrollably. Not all seizures cause convulsions. The signs and symptoms of seizures vary depending on the type (Prasad, 2013).The most common type of seizure is convulsive (60%), Two-thirds of these begin as focal seizures and become generalized while one third begin as generalized seizures (National Institute for Health and Clinical Excellence (January, 2012). The remaining 40% of seizures are non-convulsive, an example of which is absence seizure (Hughes, 2009). A febrile seizure (FS), also known as a fever fit or febrile convulsion, is a seizure associated with a high body temperature but without any serious underlying health issue. They most commonly occur in children between the ages of 6 months and 5 years. Most seizures are less than five minutes in duration and the child is completely back to normal within sixty minutes of the event (Graves *et al.,* 2012). It is the most common convulsive disorder in children, and it is defined as a seizure accompanied with fever and without system infection, which occurs in infants and children of age 6 through 60 months (APA, 2011). Febrile seizures affect 2-10% of children before the age of 5 years old (Perkin, 2008). They are more common in boys than girls (Prasad, 2013).

In 50% of children, the first attack of febrile seizures occurs in the second year of life,

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and in 90% of children, before the age of 3 years (Verity and Golding, 1991). Febrile seizures may run in families; diagnosis involves verifying that there is no infection of the brain and there are no metabolic problems. There are two types of febrile seizures: simple febrile seizures and complex febrile seizures. (EEG) is typically not needed for the diagnosis. Examination to determine the source of the fever is recommended. In otherwise healthy looking children a lumbar puncture is not necessarily required (Graves *et al.,* 2012). The risk of developing unprovoked seizures after a febrile seizure is estimated to be 2% to 5% (Annegers *et al.,* 1987). The predictive risk factors for the development of epilepsy are developmental delay or an abnormal neurologic examination finding before the onset of the febrile seizure (Vestergaard *et al.,* 2007). After a single febrile seizure there is a 15-70% chance of another one (Graves *et al.,* 2012).

The aim of this study is to study the occurrence of febrile seizure after 5 years of age.

Materials and Methods

This study was conducted in The Pediatric Neurology Unit, Ain Shams University, Faculty of Medicine in the period from 2011 to 2015. (50) Patients were prospectively included in the study and grouped into two separate groups. All patients were having febrile seizures that occurred after 5 years of age. Group 1 consisted of 31 patients who had their first febrile seizure after 5 years of age, and group 2 consisted of 19 patients in whom febrile seizure persisted after 5 years of age. A febrile seizure was defined according to the definition of The American Academy of Pediatrics (AAP, 2011). We estimated the demographic data (age, gender and family history of febrile seizure and epilepsy) ,clinical data (degree of fever, duration, semiology and frequency of seizures), magnetic resonance imaging (MRI) findings , electroencephalography (EEG) findings and psychomotor development test results of the two groups. Patients with history of afebrile seizure, having symptomatic seizures, pathological neurologic background and progressive system illness were excluded.

Late-onset febrile seizure was that occurred after the age of five years old. Persistent febrile seizure was defined as that occurred both before and after 5 years of age. Complex febrile seizure was defined as either focal or multiple seizures, seizures longer than 15 min or a combination of these. Simple febrile seizure was defined as a single generalized seizure within 24 h and seizures less than15 min (AAP, 2011). lesions of the white matter or hippocampal malrotations were defined as abnormal MRI finding . Peak fever was categorized into a low fever group (< 39 °C) and a high fever group (≥39 °C). Any abnormality on background activity or any epileptiform discharges in the EEG were defined abnormal.

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 analyze the differences between measurements such as the total number of seizures and the mean age. chi-square test was used for the duration of seizures, parameters of EEG, MRI, type of seizure, type of febrile seizures, family history of febrile seizures, family history of epilepsy, consanguinity, WISC-R evaluation, 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.

Results

50 patients (21 females and 29 males) were enrolled in the study. The mean follow-up period of the patients was 1 to 4 years. The demographic and clinical features are shown in Table 1and 2 respectively.

Evaluation of patients with late-onset FS (group 1, n = 31)

Group 1: Consisted of 14 (45.2%) females and 17 (54.8%) males, with a mean age of 7.85 ± 2.06 years. 3 patients (9.7%) had a prenatal history of maternal smoking, and 3 patients (9.7%)were delivered prematurely. 28 patients (90.3%) were vaccinated with diphtheria and tetanus before the development of seizure. The parents of 6 patients (19.4%)

had positive consanguinity. 7 patients (22.6%) had a family history of FS. 23 patients (74.2%) had a peak fever temperature of up to 39 °C, whereas 8 patients (25.8%) had a peak fever temperature greater than 39 °C. also, 5 patients (16%) had a history of afebrile seizures.3 patients (9.7%) had a duration of seizures> 15 minutes and 28 patients (90.3%) had a duration of seizures< 15 minutes. The total number of seizures in this group was 2.1 ± 0.78.

Table 1: Shows demographic features of both groups of patients:

Demographic Features	Group 1 (n = 31) patients who had their first FS after 5 years of age	Group 2 (n = 19) patients in whom FS persisted after 5 years of age	P Values
Mean age (years ± SD)	7.85 ± 2.06	8.32 ± 2.03	>0.05
Gender Male Female	 17 (54.8 %) 14 (45.2 %)	 12 (63.2 %) 7 (36.8 %)	>0.05
Prenatal History of maternal smoking Yes No	 3 (9.7 %) 28 (90.3 %)	 2 (10.5 %) 17 (89.5 %)	>0.05
History of vaccination Yes No	 28 (90.3%) 3 (9.7%)	 18 (94.7%) 1 (5.3 %)	>0.05
Premature delivery	3 (9.7%)	2 (10.5 %)	>0.05
Family History + Ve -Ve	 7 (22.6 %) 24 (77.4%)	 9 (47.4%) 10 (52.6 %)	>0.05
Consanguinity +Ve -Ve	 6 (19.4%) 25 (80.6%)	 5 (26.3%) 14 (73.7 %)	>0.05
Presence of Afebrile seizure Yes No	 5 (16 %) 26 (84%)	 5 (26.3%) 14 (73.7%)	>0.05
Total Number Of Seizures	2.1 ± 0.78	4.6 ± 1.46	>0.05
Peak Of Fever 37 – 38 ≥ 38 – 39 ≥ 39 – 40 ≥ 40	 6 (19.4 %) 17 (54.8%) 7 (22.6 %) 1 (3.2 %)	 3 (15.8%) 8 (42 %) 7 (36.8 %) 1 (5.4 %)	>0.05
Duration of seizure >15 minutes < 15 minutes	 3 (9.7%) 28 (90.3 %)	 2 (10.5 %) 17 (89.5%)	>0.05

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

Evaluation of patients in whom FS persisted after 5 years of age (group 2, n = 19)

Group 2:

Consisted of 7 (36.8%) females and 12 (63.2%) males, with a mean age of 8.32 ± 2.03 years. 2 patients (10.5%) had a prenatal history of maternal smoking, and 2 patients (10.5%) were delivered prematurely. 18 patients(94.7%) were vaccinated with diphtheria and tetanus before the development of seizure. The parents of 5 patients (26.3%) had positive consanguinity. 9 patients (47.4%) had a family history of FS. 11 patients (57.8%) had a peak fever temperature of up to 39 °C, whereas 8 patients (42.2%) had a peak fever temperature greater than 39 °C. also, 5 patients (26.3%) had a history of afebrile seizures.2 patients (10.5%) had a duration of seizures> 15 minutes and 17 patients

(89.5%) had a duration of seizures< 15 minutes. The total number of seizures in this group was 4.6 ± 1.46.

Table 2: Shows Clinical features of both groups of patients:

Demographic Features	**Group 1 (n = 31)** patients who had their first FS after 5 years of age	**Group 2 (n = 19)** patients in whom FS persisted after 5 years of age	**P Values**
Type Of Seizures			
Generalized	25 (80.6 %)	17 (89.5 %)	>0.05
Focal	5 (16.1 %)	1 (5.25 %)	
Secondary Generalized	1 (3.3 %)	1 (5.25 %)	
Semiology Of seizures			
Tonic	6 (19.35 %)	3 (15.8 %)	>0.05
Clonic	2 (6.45 %)	1 (5.25 %)	
Tonic – Clonic	21 (67.7 %)	14 (73.7 %)	
Atonic	1 (3.25 %)	1 (5.25 %)	
Dialeptic	1 (3.25 %)	0 (0 %)	
Simple Febrile seizure	25 (80.65 %)	17 (89.5%)	>0.05
Complex Febrile Seizure	6 (19.35 %)	2 (10.5 %)	
EEG – Findings			>0.05
Normal	21 (67 %)	12 (63.2 %)	
Abnormal	10 (33 %)	7 (36.8 %)	
MRI – Findings			>0.05
Normal	22 (71 %)	14 (73.7 %)	
Abnormal	9 (29 %)	5 (26.3 %)	
Epilepsy			>0.05
Yes	28 (90.3 %)	17 (89.5 %)	
No	3 (9.7 %)	2 (10.5 %)	
WISC-R: Wechsler			>0.05
Normal	21 (67 %)	12 (63.2 %)	
Abnormal	10 (33 %)	7 (36.8 %)	

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

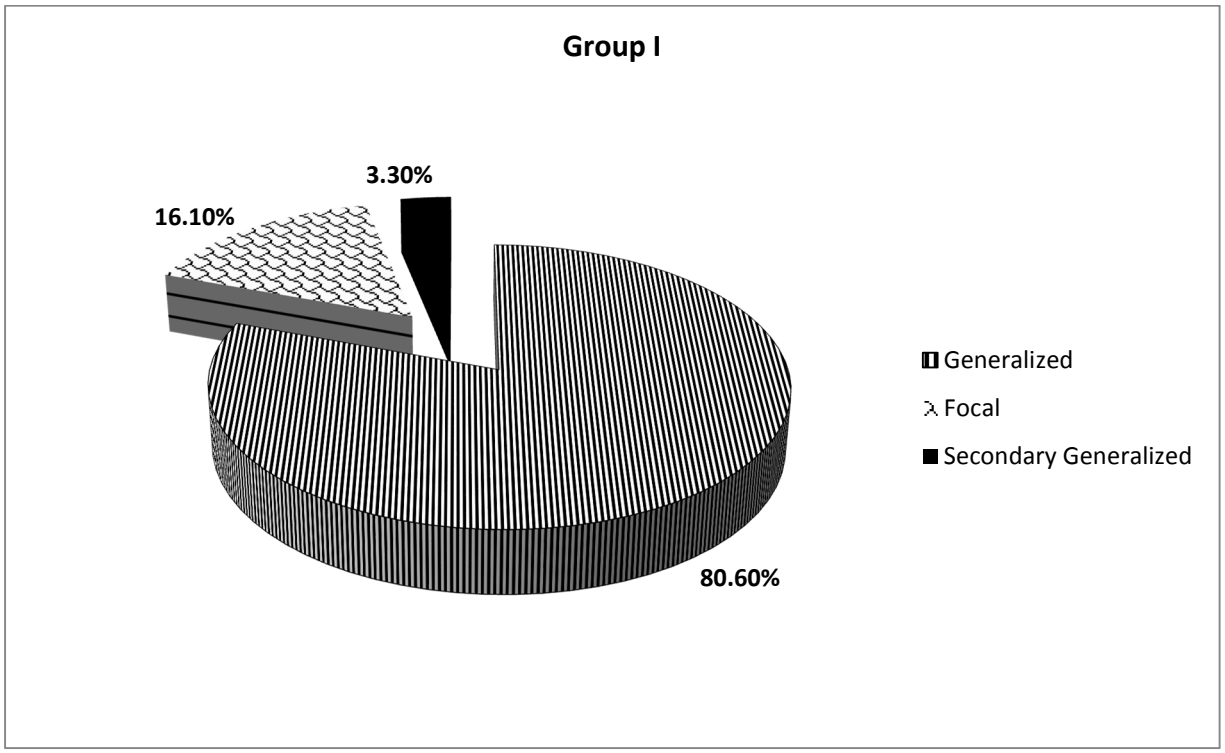

Fig. 1: Shows the percentages of types of seizures among group 1

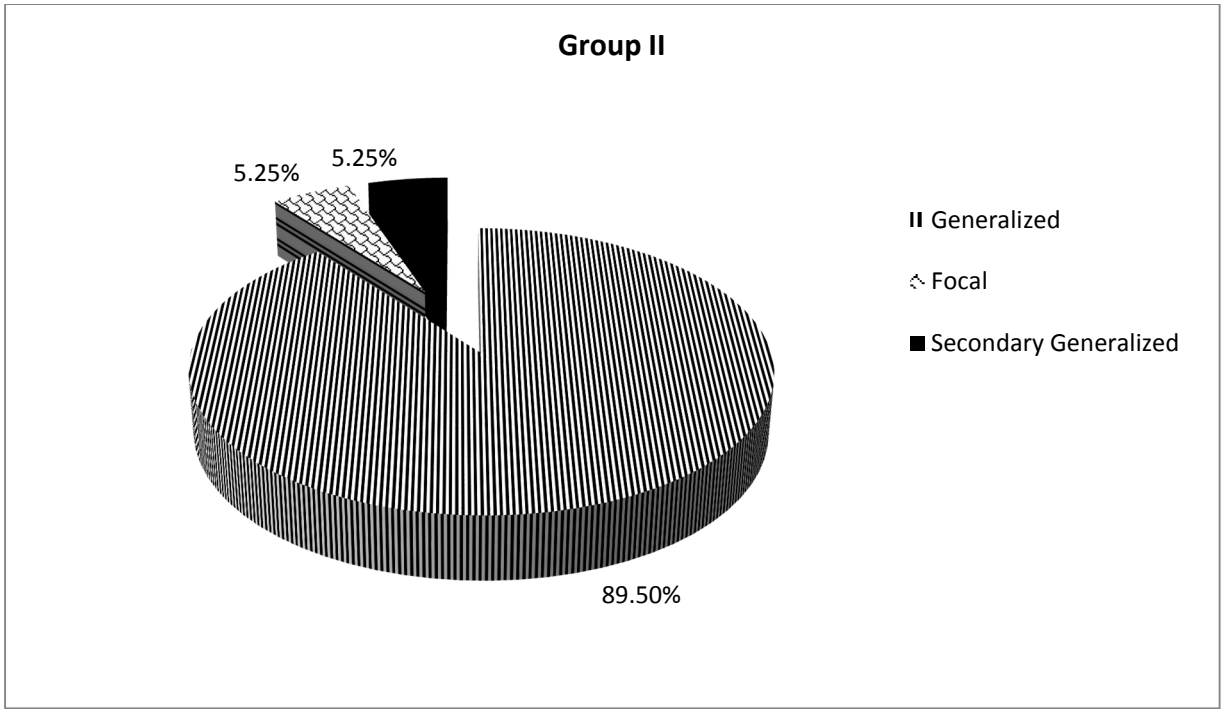

Fig. 2: Shows the percentages of types of seizures among group 2

Group 1:

Concerning the type of seizure, there were 25 patients (80.6%) having generalized seizures, 5 patients (16.1%) having focal seizures and 1 patient (3.3%) with secondary generalized seizures. Concerning the semiology of seizures, there were 6 patients (19.35 %) with tonic seizures, 2 patients (6.45 %) with clonic seizures, 21 patients (67.7 %) with tonic –clonic seizures, 1 patient (3.25 %) with atonic seizures and 1 patient (3.25 %) with dialeptic seizures. Also, there were 25 patients (80.65 %) with simple febrile seizure and 6 patients (19.35 %) with complex febrile seizure. Concerning the EEG findings, we found 21 patients (67 %) with normal EEG findings and 10 patients (33 %) with abnormal EEG findings. concerning the MRI findings, there were 22 patients (71 %) with normal MRI findings and 9 patients (29 %) with abnormal findings. Also, there were 28 patients (90.3 %) with epilepsy and 3 patients (9.7 %) with no epilepsy. And lastly, concerning the WISC-R: Wechsler, there were 21patients (67 %) normal and 10 patients (33 %) abnormal.

Group 2:

Concerning the type of seizure, there were 17 patients (89.5 %) having generalized seizures, 1patient (5.25%) having Focal Seizures and 1 patient (5.25%) with Secondary Generalized Seizures. Concerning the semiology of seizures, there were 3 patients (15.8 %) with tonic seizures, 1patient (5.25 %) with clonic seizures, 14 patients (73.7 %) with tonic –clonic seizures, 1 patient (5.25 %) with atonic seizures and 0 patient with dialeptic seizures. Also, there were 17 patients (89.5 %) with Simple Febrile seizure and 2 patients (10.5 %) with Complex Febrile Seizure. Concerning the EEG findings, we found 12 patients (63.2 %) with normal EEG findings and 7 patients (36.8 %) with abnormal EEG findings. concerning the MRI findings, there were 14 patients (73.7 %) with normal MRI findings and 5 patients (26.3 %) with abnormal findings. Also, there were 17 patients (89.5 %) with epilepsy and 2 patients (10.5 %) with no epilepsy. And lastly, concerning the WISC-R: Wechsler, there were 12 patients (63.2 %) normal and 7patients (36.8 %) abnormal. There was no statistically significant difference between the two groups in terms of mean age, gender, prenatal

history, natal history, history of vaccination, consanguinity, family history of epilepsy, presence of afebrile seizure, type of seizure, semiology of seizure, EEG and MRI findings and evaluation of Wechsler Intelligence Scale for Children, Revised (WISCR). There was a statistically significant difference between the groups for family history of febrile seizures. Peak fever also did not significantly differ between the groups. The presence of afebrile seizure was not statistically associated with the total number of seizures, type of seizure, type of febrile seizures, gender, consanguinity and family history of febrile seizures.

Discussion

In this study, we evaluated the risk of subsequent epilepsy in children who had the first febrile seizure after 5 years of age. Our results demonstrated that the overall risk of epilepsy following febrile seizures was 89.9% (n = 50). However, the number of patients was not enough to estimate the real incidence of afebrile seizures or epilepsy in our study. Febrile seizures are the most common form of childhood seizure, and its prognosis is generally good. The risk of developing epilepsy after febrile seizures is controversial. Previous studies reported the incidence of epilepsy after febrile seizures at 2% to 5% (Vestergaard *et al.,* 2007; Annegers *et al.,* 1987).

Study done by Neligan *et al., 2012* demonstrated that the risk of developing epilepsy following febrile seizures was 2% to 10%. Verotti *et al.,* (2000) evaluated children with febrile seizures occurring or persistent after 5 years of age. They found that children (n = 20) with febrile seizures after 5 years of age could have a two- to three-fold risk of developing subsequent unprovoked seizures compared to children under 5 years of age with seizures and fever. Pavone *et al*., (1989) found that the risk of epilepsy in children who have febrile seizures after 6 years of age was 15.8% in a 5-year follow-up period. Our results are consistent with the literature.

The pathogenic mechanism or a cause-effect relationship between febrile seizures and epilepsy is unclear. Some recent studies have pointed to a genetic relationship between FS and epilepsy (Abou-Khalil *et al.,* 2007; Dube *et al.,* 2009). Similarly*,* Burgess, (2005) and discussed some of the potential mechanisms that have been recently revealed to link mutant ion channel genes to generalized epilepsy with febrile seizures plus (GEFS+). Vestergaard *et al.,* (2007) reported that siblings of children with febrile seizures frequently display epilepsy, even if they did not experience febrile seizures. In addition to genetic predispositions, the FEBSTAT MRI study (Shinnar *et al.,* 2012) also showed that acute febrile status epilepticus might cause acute hippocampal injury.

Our study showed that the incidence of subsequent epilepsy after febrile seizures was higher and It is independent of gender, meanage, prenatal history, natal history, history of vaccination, consanguinity, family history of epilepsy, presence of afebrile seizure, type of seizure, duration of seizure, semiology of seizure, peak fever and EEG and MRI findings in our total cohort. One of the main limitations of our study is the small sample size. Therefore, we cannot confirm that the previous factors definitely do not increase the risk of epilepsy. Previous studies have shown that the risk factors for unprovoked seizures after febrile seizures are the onset of febrile seizures at an early age, complex febrile seizures, neurodevelopmental abnormalities, abnormal EEG, and a family history of epilepsy (Hwang *et al.,* 2015; Pavlidou and Panteliadis, 2013). Our results demonstrated that prolonged febrile seizure (>15 min) is not a risk factor for developing epilepsy. Similarly, Sapir *et al.* (2000) reported that none of their patients with prolonged febrile seizures later developed epilepsy. A recent study concluded that a prolonged febrile seizure is the result of a previous insult to the hippocampus and not the cause of it (Scott *et al.,* 2006). On the other hand, neuroimaging and animal studies demonstrated acute swelling and edema of the hippocampus and that hyperthermia-induced seizures may cause long-lasting modifications of the channels, synapses and neuronal networks within the hippocampus, leading to sustained dysfunction of these cells and a decreased seizure threshold after prolonged febrile seizures (Chen *et al.,* 1999; Van Landingham *et al.,* 1998; Cendes *et al.,* 1993).

Conclusion

Childhood febrile seizures are benign and self-limiting but epilepsy is the primary serious complication of febrile seizures, especially if the first febrile seizure occurs at an uncommon age. We

can confirm that febrile seizure can occur or continue after the age of 5 years old and may be a warning sign of epilepsy; thus, these children may need special attention. However, further studies with a larger cohort are needed to evaluate the risk of epilepsy in these patients.

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