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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. 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, electroencephalograms (EEGs), radiologic images 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, retrospectively in the period between 2011 and 2015. We divided patients into two groups; Group 1includes patients who had first febrile seizure after age of 5 years old, and group 2 includes patients whose febrile seizures persisted after age of 5 years old. Statistical analysis: Study data were analyzed by Fisher's exact test and Pearson's chi-square test. Results: In this study, including 50 patients, afebrile seizure was seen in 10 (20%) of them and 45 patients (90%) were diagnosed as epilepsy in their follow-up examination. Incidence of subsequent epilepsy was not related to age, gender, family history of epilepsy, presence of afebrile seizure, type of seizure, type of febrile seizure, seizure duration, seizure semiology, peak fever, EEG and magnetic resonance imaging (MRI) findings in our total cohort. Conclusion: Febrile seizures after 5 years of age are usually nonsignificant, but may recur and augment risk of future epilepsy in those patients. So, close follow-up is important and more studies with sufficient cohort are needed to demonstrate predisposing causes and occurrence of epilepsy in those patients.

Key words: Febrile seizure, Child health, Unprovoked seizures, Subsequent epilepsy.

Introduction

Seizures are symptoms of brain affection. They occur due to sudden, bizarre electrical brain activity. Not all seizures cause convulsions and uncontrollable body shaking as most of people think. The signs and symptoms of seizures vary depending on the type (Prasad, 2013). Convulsive seizures are the most frequently seen with a percentage of (60%). Two-thirds of these begin as focal seizures and become generalized while one third start as generalized seizures (National Institute for Health and Clinical Excellence (January 2012). The other 40% of seizures are non-convulsive, as in absence seizure (Hughes, 2009*).* A febrile seizure (FS) or febrile fit or convulsion, is a seizure that occurs with high body temperature without any serious underlying health problem. They usually take place in children between the ages of 6 months and 5 years. Majority of them happen in not more than five minutes and the child returns normal within sixty minutes of the seizure (Graves *et al.,* 2012). It is defined as a seizure occurring in combination with fever with no system infection and it is the most frequent convulsive disorder in pediatric age group affecting infants and children aging from 6 to 60 months (APA, 2011). They affect 2-10% of children before reaching 5 years old (Perkin, 2008) and more common in males than females (Prasad, 2013). In about 50% of patients, the first attack of febrile seizures is seen in the second year of life and reach to about 90% before the age of 3 years and usually run in families (Verity and Golding, 1991). To confirm the diagnosis, there should be no infection of the brain nor metabolic problems. Febrile seizures are 2 types: simple febrile seizures and complex febrile seizures. (EEG) and lumbar puncture are not mandatory for diagnosis in healthy

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looking children while, examination to determine the cause of fever is recommended (Graves *et al.,* 2012). Possibility of having unprovoked seizures after a febrile seizure is found to be 2% to 5% (Annegers *et al.,* 1987*)*. Developmental delay and abnormal neurologic examination finding before the onset of the febrile seizure are prophetical risk factors for the development of epilepsy (Vestergaard *et al.,* 2007). After a single febrile seizure there is a 15-70% chance of a second one (Graves *et al.,* 2012).

Aim of our study is to estimate 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 girls and 29 boys) participated in our study. The mean follow-up period was 1 to 4 years. The demographic and clinical data are demonstrated in Table 1and 2 respectively.

Estimation of late-onset FS children (group 1, no. = 31)

Group 1: includes 14 (45.2%) girls and 17 (54.8%) boys, with a mean age of 7.85 ± 2.06 years. 3 children (9.7%) born to smoking mothers; 3 (9.7%) were premature delivery; 28 (90.3%) were vaccinated with diphtheria and tetanus before occurrence of seizure. Consanguinity was positive in parents of 6 patients (19.4%). 7 patients (22.6%) had a family history of FS. 23 (74.2%) had maximum fever temperature of up to 39 °C, whereas 8 (25.8%) had maximum fever temperature > 39 °C. also, 5 (16%) had a history of afebrile seizures.3 (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 (no. = 31) children having first FS after age of 5 years old.	Group 2 (no. = 19) children with FS persisted after age of 5 years old.	P
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.

Estimation of FS persisted after age of 5 years old (group 2, no. = 19)

Group 2: includes 7 (36.8%) girls and 12 (63.2%) boys, with a mean age of 8.32 ± 2.03 years. 2children (10.5%) born to smoking mothers, 2 (10.5%) were premature delivery. 18(94.7%) were vaccinated with diphtheria and tetanus before occurrence of seizure. Consanguinity was positive in parents of 5 patients (26.3%); 9 (47.4%) had a family history of FS; 11(57.8%) had maximum fever temperature of up to 39 °C, while 8 (42.2%) had maximum fever temperature > 39 °C. also, 5 children (26.3%) had a history of afebrile seizures; 2 (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.

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.

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

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

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

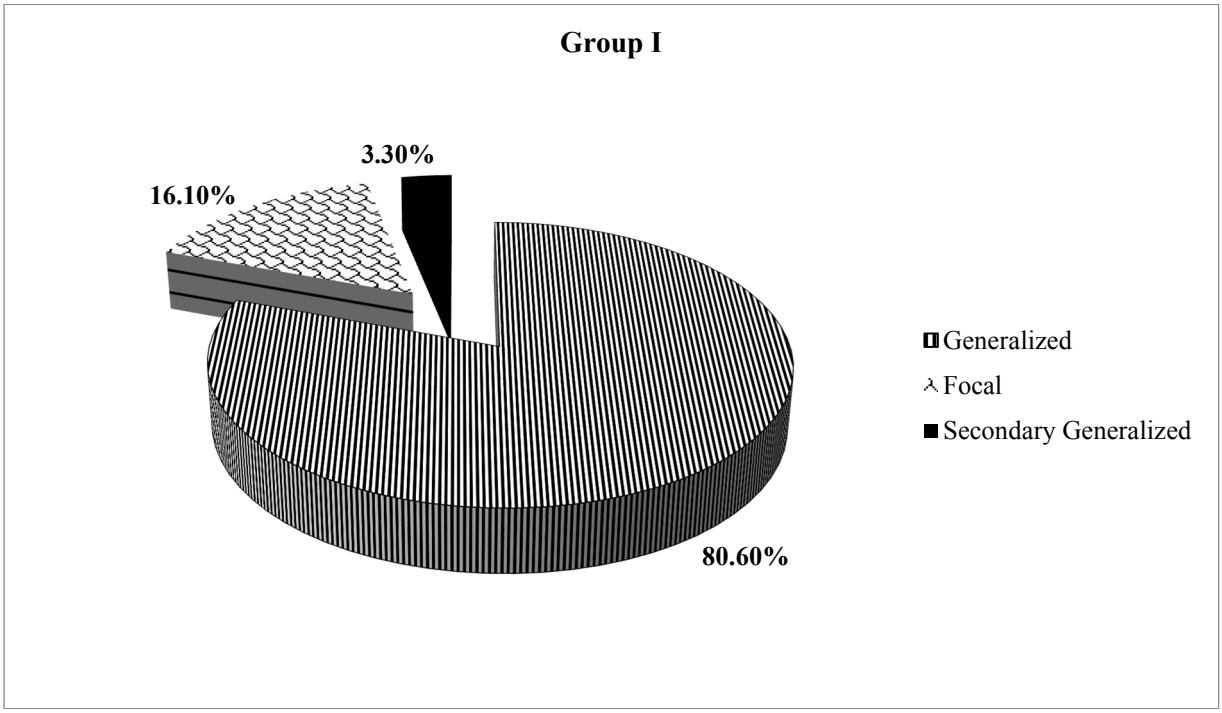

Fig. 1: Shows the percentages of types of seizures among group 1

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. No statistically marked difference was found between both groups as regards gender ,mean age, peak fever, prenatal history, natal history, family history of epilepsy, vaccination history, consanguinity, occurrence of afebrile seizure, seizure type, seizure semiology, EEG, MRI findings and evaluation of Wechsler Intelligence Scale for Children, Revised (WISCR). a statistically marked difference between both groups concerning family history of febrile seizures. No statistical correlation was found between occurrence of afebrile seizure and seizures' total number, seizure type, febrile seizures' type, gender, consanguinity and family history of febrile seizures.

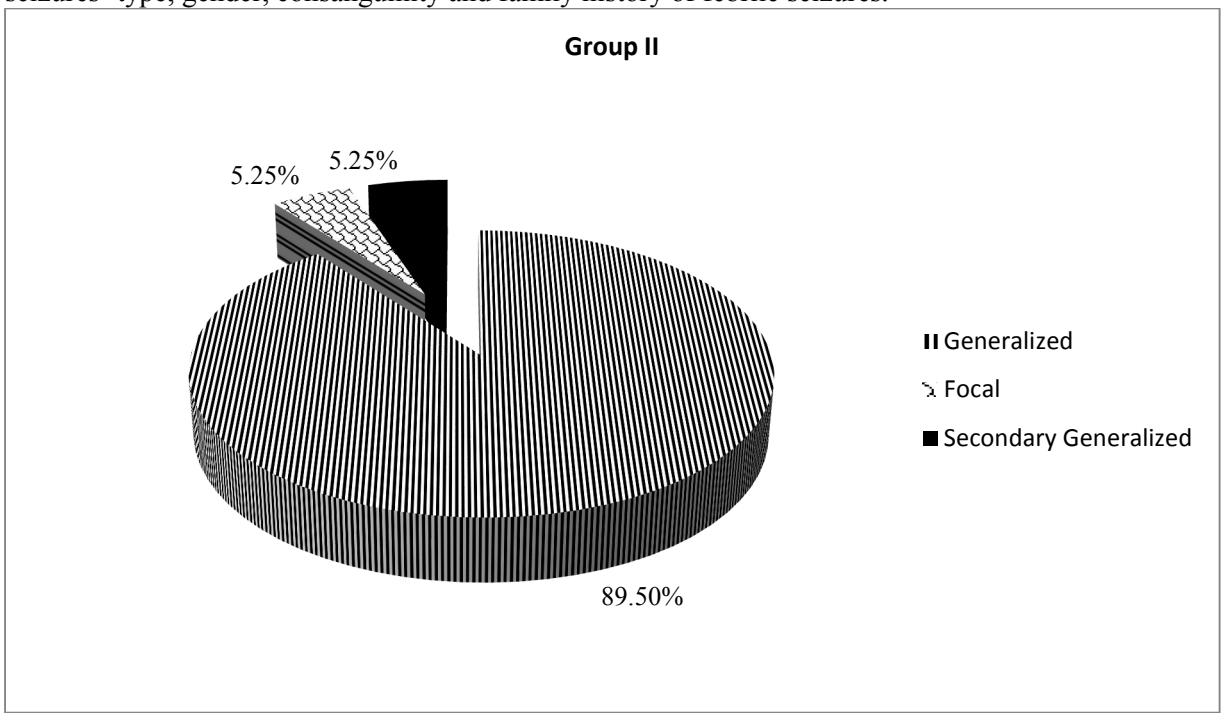

Fig. 2: Shows the percentages of types of seizures among group **2**

Discussion

In our work, we estimated the possibility of epilepsy development in patients who had the first febrile seizure after the age of 5 years old. Our results showed that estimated possibility of epilepsy after febrile seizures was 89.9% (no. = 50); in spite of non-sufficient number of patients to measure accurate percentage of epilepsy in our cohort. Febrile seizures are the most frequent type of pediatric epilepsy, it usually has a satisfying prognosis. The possibility of epilepsy occurrence after febrile seizures is debatable as it was estimated in previous studies to be 2% to 5% (Vestergaard *et al.,* 2007) *(*Annegers *et al.,* 1987).

Neligan *et al.* (2012) in his study, found that possibility of getting epilepsy after febrile seizures was 2% to 10%. Also, Verrotti *et al.* (2000) found that patients with febrile seizures happening or continuous after the age of 5 years old may have 2 to 3-times possibility of getting following unprovoked seizures in comparison to patients > 5 years old with seizures and fever. Our results agreed to results of Pavone et al. (1989) who showed that possibility of having epilepsy in children who have febrile seizures after the age of 6 years old was 15.8% in a 5-year follow-up duration. The exact correlation between febrile seizures and epilepsy is unknown. Some researchers suggested genetic background between FS and epilepsy (Abou-Khalil *et al.,* 2007; Dube *et al.,* 2009). Also, Burgess, 2005) mentioned basic theories that have been recently found to correlate mutant ion channel genes to generalized epilepsy with febrile seizures plus (GEFS+). Vestergaard *et al.* (2007) demonstrated that brothers of patients with febrile seizures usually develop epilepsy, even if they did not experience febrile seizures. In addition to genetic susceptibility, the FEBSTAT MRI study Shinnar *et al.* (2012) also declared that acute febrile status epilepticus may lead to acute hippocampal damage.

This research found that the occurrence of epilepsy following febrile seizures was great and it was unrelated to gender, mean age, prenatal history, natal history, history of vaccination, consanguinity, family history of epilepsy, presence of afebrile seizure, seizure type, seizure duration, seizure semiology, peak fever, EEG and MRI results in this study. Small sample size of our research was one of the major restrictions of our study. So, other previous factors may be involved in increasing possibility of epilepsy. Other studies demonstrated that underlying causes for unprovoked seizures following febrile seizures are early age of onset, complex febrile seizures, neurodevelopmental problems, abnormal EEG, and a family history of epilepsy (Hwang *et al.,* 2015; Pavlidou and Panteliadis, 2013). Our results have shown that persistent febrile seizure (>15 min) is not an alarming sign of getting fits. Also, Sapir *et al.* (2000) found that none of their patients with persistent febrile seizures later got epilepsy. New research found that persistent febrile seizure is the outcome of an existing hippocampal injury (Scott *et al.,* 2006). Again , neuroimaging and animal studies showed acute hippocampal swelling and edema and seizures caused by hyperthermia can lead to persistent alterations of hippocampal channels, synapses and neuronal networks, resulting in continuous disability of those cells and a lowered seizure threshold after persistent febrile seizures (Chen *et al.,* 1999; Van Landingham *et al.,* 1998*;* Cendes *et al.,* 1993).

Conclusion

Childhood febrile seizures are not harmful and self-limiting but epilepsy is the major dangerous sequalae of febrile seizures, particularly if the first febrile seizure happens at an unfamiliar age. We can say that febrile seizure can happen or continue after the age of 5 years old and can be an alarming

alert of epilepsy; therefore, those patients may require particular care. So, more researches with bigger cohort are needed to estimate possibility of epilepsy in those children.

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