Original Article

Association of Epilepsy in Children Experiencing Febrile Seizure: Findings from National Institute of Neuroscience, Bangladesh

Banita Mistry[1], Rajib Nayan Chowdhury[2], Dipa Saha[3], Mohammad Enayet Hussain[4], Kazi Selim Anwar[5], A.F. Al-Masum Khan[6], Shameem Ara Begum[7], Yamin Shahriar Chowdhury[8]

Abstract

Background: Febrile seizure-(FS) remains the commonest benign convulsive childhood event. Prolonged-FS may have long-term consequences, including increased risk of subsequent-epilepsy.

Objective: To assess if there is any association among epilepsy and epilepsy syndrome with FS.

Methodology: This cross-sectional study was conducted in Epilepsy Clinic, National Institute of Neurosciences, Bangladesh, from January-June, 2021 involving one hundred 1-18 years-old-children diagnosed as epilepsy without secondary causes (intracranial space occupying lesion, head-trauma, CNS-infection, stroke). Patients were clinically evaluated thoroughly and were divided into two groups (Gp): Gp-A having a history of (H/O) FS and Gp-B, without FS. Demographically, clinical profile and electrophysiological-parameters were compared between the two groups for association with H/O FS. Pre-checked/cleaned-data were analyzed using SPSS.V.22.0 for proportional differences, taken p<.05 as significant (95%-CI). It was distributed nearly equally among both sexes, irrespective of FS. Although generalized epilepsy was common in both 12/14 (85.71%) Gp-A Vs. 54/86 (62.79%) Gp-B; epilepsy syndrome (infantile spasm, LGS, JME, JAE) revealed significantly more among non-FS-children than genetic epilepsy FS+ was more in FS group (p = 0.04). On EEG, generalized slowing [2/14 (14.28%)], generalized discharge [3/14 (21.42%) and features of encephalopathy [3/14 (21.42)] was observed more in patients with H/O FS, than non-FS.

Conclusion: In contrast to other types of epilepsy, our study revealed that genetic epilepsy febrile seizures + was associated with epileptic children who had H/O FS.

Key Word: Epilepsy, Febrile seizure, generalized epilepsy; Association

Introduction:

Febrile seizures (FS) are defined as seizures occurring in childhood accompanied by a temperature of 38°C or higher without evidence of an intracranial infection or defined seizure. It is the most common seizure type in children from 5 months to 5 years with a frequency of 2 to 5%, being higher in the second year of life.[1] The growth and development usually remain unaffected in children with a history of FS. Although FS are considered to be benign, recent evidence suggests that a small number of children with FS may develop recurrent FS or epilepsy. The prevalence of FS does not vary in different studies.[2,3] Variation of prevalence of FS depends on geographic location and is higher in Japan and Guam.

Although FS are not epilepsy, it may be the first presentation of subsequent epilepsy. It is difficult to predict who will develop epilepsy in future having FS in children. Epilepsy after FS was found to be 2% to 7%, four to five times more than general pediatric population. Published data are limited on the prevalence of epilepsy in association with FS in Bangladeshi children. Thus, this study was conducted on children at Epilepsy clinic, National Institute of Neurosciences, (NINS) Dhaka, to give an impression of the problem among children. This

1. Assistant Professor, Pediatric Neurology, National Institute of Neurosciences & Hospital (NINS)
2. Professor and Head, Dept. of Neurophysiology. NINS
3. Associate Professor, Pediatrics Neurology, Addin Women's Medical College Hospital
4. Associate Professor, Neurology. NINS.
5. Head, Ad-din Research Unit, Ad-din Women's Medical College (AWMC)
6. Assistant Professor, Neurology. NINS
7. Assistant Professor, pediatric Neurology. NINS
8. Assistant Professor, Pediatric Neurology. NINS

Correspondence:

1. * Dr. Banita Mistry, FCPS (Pediatrics) FCPS (pediatric Neurology and development), Assistant Professor, Pediatric Neurology. National Institute of Neurosciences & Hospital (NINS) Sher-E-Bangla Nagar, Dhaka-1207. E-mail: banitamistry08 @yahoo.com, Mobile: +88-0181-945-2684
2. *Dr. Dipa Saha, Associate Professor, Pediatrics Neurology, Addin Women's Medical College Hospital, 2, Bara Magh Bazar, Dhaka – 1217, Mobile: 01717337891, Email: dipasaha182@gmail.com

Received Date : 20 February, 2023
Accepted Date : 15 April, 2023

study aimed to highlight the characteristics of epilepsy in children with history of (H/O) FS. In the present study, we evaluated the association between FS and epilepsy and also a possible association between FS and any specific type of epilepsy/ syndrome.

Methodology:

Hospital set-up and patient population:

This cross-sectional study was conducted from January to July, 2021 at Epilepsy Clinic, National Institute of Neurosciences (NINS), Dhaka, being the only national level hospital on neurology in Bangladesh.

Detailed methodology, clinical evaluation and neurological investigations:

After taking informed consent, 100 children aged 1 to 18 years diagnosed as Epilepsy according to international league against epilepsy (ILAE) were enrolled for this study. However, secondary causes of seizure (intracranial space occupying lesions, head trauma, CNS infection and stroke) were excluded. All children were evaluated by the pediatric-neurologists, when detail history, clinical examination and necessary investigations, like, EEG, CT/MRI of Brain were performed. The criteria proposed by the International Classification of febrile Seizures (FS) and Epilepsy & Epilepsy Syndromes were considered to classify FS and epilepsy in our study.

Randomized grouping based on clinical symptomatology and neurological investigations:

Clinico-epidemiological history related to age at onset of FS, duration, type, frequency of FS, age of onset of epilepsy, its type, family history of FS/epilepsy, consanguinity, developmental history, birth and vaccination history were noted. As the children were clinically evaluated thoroughly, they were divided into two groups (Gp): Gp-A having a history of (H/O) FS and Gp-B, without FS. Demographic, clinical profile and electrophysiological-parameters were compared.

Data management and statistical analysis:

All the demographic status, clinical profile and electrophysiological-parameters from both FS- and non-FS groups were compared for the existing association these 2- groups. Pre-checked/cleaned-data were analyzed using SPSS.V.23.0. Analysis was performed to find out the association of epilepsy among the children who had H/O FS and who had no H/O of FS. Continuous data with normal distribution were analyzed in mean, standard deviation and the data those were non-normally distributed used, median and inter-quartile range with minimum and maximum ranges. Categorical or discrete data was summarized in frequency distribution (counts and percentages). For end points analysis, chi square test was used for categorical variables (comparing proportions) and an analysis of variance (one-way ANOVA Test) for continuous outcomes. Finally, multiple logistic regressions were performed to understand the independent association of epilepsy with FS. In the regression model, epilepsy was the dependent variable and significant associated factors with epilepsy were considered as the independent variables. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Odds ratios and their 95% confidence intervals were calculated to evaluate strength of the association.

Ethical Clearance:

The institutional/ Ethical review committee of National Institute of Neurosciences and Hospital approved the study prior to launching. Before enrolling parents were explained about the purpose of the study and written informed consent was sought from the participant's guardian.

Result:

A total of 100 children aged 1 to 18 years diagnosed as Epilepsy (ILAE) without any secondary causes (ICSOL, head trauma, CNS infection, stroke) were enrolled. Among the study cases mean age was 9.98 ± 5.75 years, most of them were female 58 (58%), 33 (33%) cases had developmental delay and 3 (3%) had family history of epilepsy. The mean age of epilepsy onset was 5.44 ± 5.26 years and generalized epilepsy were common epilepsy type 66 (66%) followed by focal 30 (30%), unknown 4 (4%) and 10 (10%) had epilepsy syndrome. Infantile spasm 4(4%), LGS 2 (2%), JME 2(2%), GEFS+ 1(1%), JAE 1 (1%) were common epilepsy syndrome here **(Table I).**

Majority of the cases had no history of FS, except 14% who had FS **(Figure 1).** All cases who had history of FS, mostly (85.71%) experiencing simple FS with tonic-clonic (50%) in nature, and 57% facing recurrent episodes with an average frequency of > 2 FS **(Table II).**

Mean (± SD) age was 8.20 ± 4.77 years in children having history of FS and 10.28 ± 5.86 years who had no FS, the male female ratio was 1:1. Epilepsy was observed more in children belonging to middle class parental families in both FS and non-FS groups. Developmental delay was higher in FS-children (33.7%) than non-FS (28.57%). On both groups most of the cases had full term delivery, Group A: 13/14(92.85%)) and Group B 80/86 (93.02%). While the mean age of epilepsy onset was 4.87± 3.97

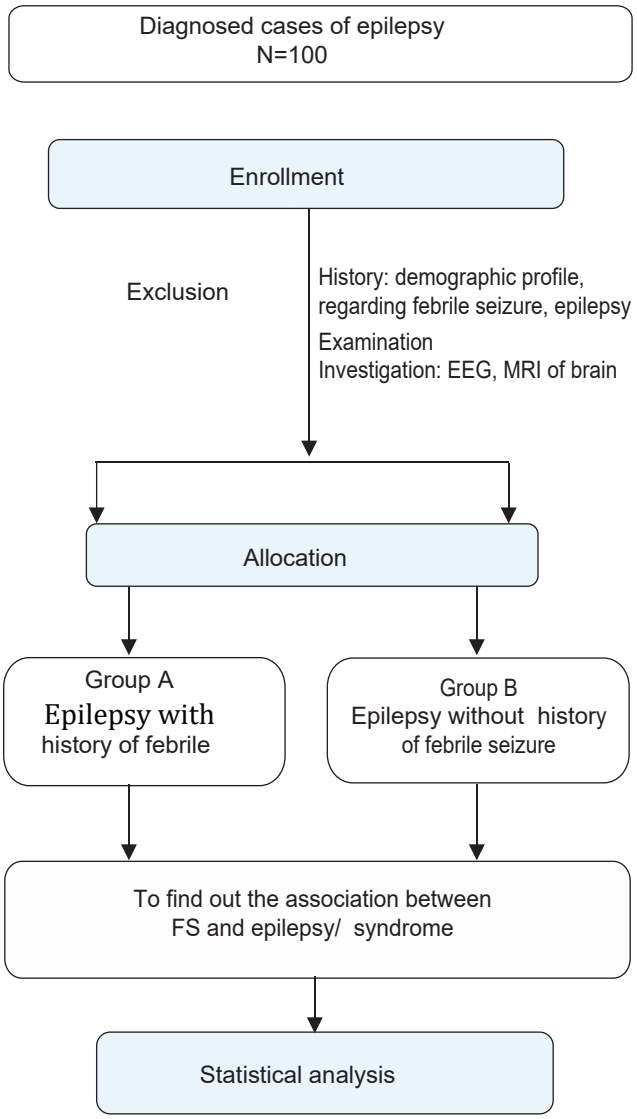

Figure 1: *Enrolment of epileptic children with or without FS*

years it was 5.54 to 5.48 years with or without FS, respectively. Generalized epilepsy was higher in both groups FS Group 12/14 (85.71%) and non FS group 54/86(62.79%), epilepsy syndrome (infantile spasm, LGS, JME, JAE) were significantly higher Non-FS group with the exception of GEFS+, and, for those, who had FS (p=0.04) more commonly. EEG revealed more focal epileptiform discharge in patients without H/O FS (48.83%) than not (35.71%), and, more generalized slowing 2/14 (14.28%), generalized discharge 3/14 (21.42%) and features of encephalopathy 3/14 (21.42) was observed in patients with H/O FS. MRI was done among 4 cases and found cerebral atrophy in 3 cases and 1 case had hippocampal sclerosis and all were in non-FS group **(Table III).**

Table I

Clinico demographic profile among the study cases (N=100)

Clinico-demographic profile	Frequency (%)
Age (Years) mean ±SD	9.98 ± 5.75
Sex	
Male	51 (51%)
Female	58 (58%)
M:F	
Socio-economic status	
Poor	35 (35%)
Middle	58 (58%)
Good	7 (7%)
Family History of epilepsy	3 (3%)
Developmental delay	33 (33%)
Epilepsy	
Age of onset	5.44 ± 5.26
Epilepsy type	
Generalized	66 (66%)
Focal	30 (30%)
Unknown	4 (4%)
Epilepsy syndrome	10 (10%)
Infantile spasm	4 (4%)
LGS	2(2%)
Juvenile myoclonic epilepsy	2(2%)
Genetic epilepsy febrile seizure plus (GEFS+)	1(1%)
Juvenile absence epilepsy	1 (1%)

Table II

Characteristics of febrile seizure among the study cases (n=14)

Febrile seizure (14)	n (%)
Types of febrile seizure	
Simple	12 (85.71)
Complex	1 (7.14)
Status epilepticus	1 (7.14)
Phenomenology	
Tonic	4 (28.57)
Clonic	1 (7.14)
Tonic-clonic	7 (50)
Version	2 (14.28)
Single febrile seizure	6 (43)
Recurrent febrile seizure	8 (57)
Frequency of febrile seizure, Mean ± SD	2.42 ± 2.20 (1-9)

Table III

Clinic demographic factors among the study cases (n=100)

Variable	Epilepsy		P-value
	Group A H/O Febrile seizure (n=14) n (%)	(Chi-Sq)Group B No H/O Febrile seizure (n=86) n (%)	
Age, Mean ± SD	8.20 ± 4.77	10.28 ± 5.86	0.212
Gender			
Male	7 (50)	44 (51)	
Female	7 (50)	42 (49)	0.565
M: F	1:1	1.04:1	
Socioeconomic status			
Poor		30 (34.88)	
Middle	5(35.71)	49 (56.97)	0.758
good	9 (64.28)	7(8.13)	
	0		
Birth history			
Preterm	1(7.14)	6(6.97)	0.545
Term	13(92.85)	80 (93.02)	
Family H/O epilepsy	1(7.14)	2 (2.32)	0.370
Developmental delay	4 (28.57)	29 (33.72)	0.470
Age of Epilepsy onset (mean± SD)	4.87± 3.97	5.54± 5.48	0.664
Duration of epilepsy, Mean ± SD	3.06 ± 2.85	4.36 ± 3.81	0.282
Epilepsy type			
Generalized	12 (85.71)	54 (62.79)	
Focal	2(14.28)	28 (33.55)	0.251
Unknown	0	4 (4.65)	
Epilepsy Syndrome			
Infantile spasm	0	4(4.65)	
LGS1	0	2(2.32)	0.04
JME2	0	2 (2.32)	
GEFS3+	1(7.14)	0	
JAE4	0	1(1.16)	
Abnormal EEG (n= 62)	9 (64.28)	53 (61.62)	0.674
Focal slowing	1 (7.14)	2(2.32)	
Generalized slowing	2 (14.28)	5 (5.81)	0.708
Epileptiform discharge			
Focal epileptiform discharge	5(35.71)	42 (48.83)	
Generalized discharge	3 (21.42)	14(16.27)	
Epileptic encephalopathy	3(21.42)	15(18.60)	0.691
MRI of brain (n= 4)			
Cerebral atrophy	-	3 (3.30)	
Hippocampal sclerosis	-	1(1.16)	-

1Lennox Gastaut syndrome, 2Juvenile myco-clonic epilepsy, 3Genetic epilepsy FS+ and 4Juvenile absence epilepsy.

Discussion:

To our knowledge this is the first from Bangladesh evidencing association of development of epilepsy with febrile seizure. However, few epidemiological studies were conducted on FS among Bangladeshi children, in addition to a number of important observations on FS that we pioneered to conduct it at the Bangladesh child Hospital and institute. Most of those cases were simple FS and their onset was below 1 year. Another study was carried out in Dhaka medical College Hospital on adult-onset epilepsy with a previous history of (H/O) where they found 29.34% epilepsy cases who had a H/O febrile seizure.

Inherent lower seizure threshold genetically predisposes child with FS for the development epilepsy. In the present study 14% of the epilepsy patients had H/O FS. A retrospective study by Sardar et al in Bangladesh found a frequency of FS of 33.7%.[9] On the other hand a prospective cohort study by Neligan et al. from United Kingdom found the incidence of subsequent epilepsy after FS to be 2-10%.[6] Similar results were found in other studies as well.

The risk of unprovoked seizure was more with children with complex FS. In the current study, most (85.71%) of the FS were found to be simple type and almost consistent to other studies.[10] However study by Almojali et al. from Saudi Arabia found a higher frequency (52.3%) of complex FS among the children who presented with their first febrile seizure. Although the frequency of simple FS is more in the present study, it revealed no significant association between the FS-type and subsequent epilepsy.

The mean age of onset of epilepsy in the present study was 4.87± 3.97 years and 5.54± 5.48 years with/without FS respectively. Some studies reported a late onset of 20 years and 18 years.[10 12] The age-related discrepancy is probably due to inclusion of patients of different ages. Generalized epilepsy was the most frequent type of epilepsy in both groups (85.71% and 62.79% respectively). This is somewhat contradictory to the findings of other studies where focal epilepsies were the most frequent type.[10 12] However, Annegers et al found equal number of generalized and focal epilepsy in their study.[5] The study on the prevalence of epilepsy in Bangladesh by Mohammad et al. found generalized epilepsy as the commonest type (67.2%).[6]

Epilepsy syndromes were significantly higher (p= 0.04) among patients without H/O FS with the exception of GEFS+ which was more common (7.14%) in children with H/O FS. Generalized epilepsies with febrile seizures plus (GEFS+) are a genetic syndrome characterized by heterogeneous epilepsy phenotypes including FS &generalized epilepsies.[17,18] Focal epilepsies can occur rarely in this syndrome.

Generalized slowing (14.28 % Vs 5.81%) and generalized discharges (21.42 % Vs 16.27%) in EEG were more frequent in patients with H/O FS which did not correlate with the study by Lee et al where focal discharges were more common.[9] According to literature focal seizure are the most common seizure disorders in adult.[19] In Bangladesh and India, however, generalized seizures outnumbered other types of seizures both in children and adult.[11,17,20] In this light of findings of this study we are further planning a prospective study to be launched soon for further clarifications.

In this study, none of the parameters of demographic profile (age, gender, prematurity, socioeconomic status and family history of epilepsy) yielded any association with the risk of subsequent development of epilepsy in children irrespective of FS status, a finding being consistent with a report by Almojali et al. Moreover, findings from several other studies reported early FS-onset, prematurity and a family history of epilepsy as risk factors for subsequent unprovoked seizures following FS.[11-13, 21-22] We assume that such differences might have occurred due to dissimilarity in study design.

Conclusion:

In contrast to other types of epilepsy, our study revealed that genetic epilepsy febrile seizures + was associated with epileptic children who had H/O FS, a large-scale prospective study will better establish the causal association between FS and epilepsy and may also denotes the risk features of FS that may predict the progression to epilepsy.

References

1. Shinnar S. Febrile Seizures and Mesial /Temporal Sclerosis. Epilepsy Curr. 2003; 3:115–118.
2. Mathai KV, Dunn DP, Kurland LT, Reeder FA. Convulsive disorders in the Mariana Islands. Epilepsia. 1968; 9:77–85.
3. Stanhope JM, Brody JA, Brink E, Morris CE. Convulsions among the Chamorro people of Guam, Mariana islands. II. Febrile convulsions. Am J Epidemiol. 1972; 95:299–304.

4. Tsuboi T. Epidemiology of febrile and afebrile convulsions in children in Japan. Neurology. 1984; 34:175–181.
5. Berg AT, Shinnar S. The contributions of epidemiology to the understanding of childhood seizures and epilepsy. J Child Neurol. 1994; 9(Suppl 2):19–26.
6. NeliganA, BellGS, GiavasiC, JohnsonAL, Goodridge DM, Shovron SD, Sander JW. (2012) Long-term risk of developing epilepsy after febrile seizures: a prospective cohort study. Neurology 78:1166–1170.
7. Robert S. Fisher, J. Helen Cross, Carol D'Souza, Jacqueline A. French Sheryl R. Haut, Norimichi Higurashi et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017; 58(4):531–542.
8. Biswas R, Munsi AS, Rahman MM, Begum N, Das RC. Clinical Profile of Febrile convulsion among admitted children in a tertiary care hospital at Dhaka city. Northern International Medical College Journal. 2015 Nov 16;7(1):101-4.
9. Sardarmh, how ladermar, Hossain m. adult onset epilepsy and history of childhood febrile convulsions: a retrospective study. J Dhaka Med Coll. 2009; 18(1) :54-57.
10. Hesdorf fer DC, Hauser WA. Febrile seizures and the risk of epilepsy.In:BaramTZ, Shinnar S, editors. Febrile Seizures. San Diego: Harcourt Inc;2002.p.63
11. Lee SH, Byeon JH, Kim GH, Eun B-L, Eun S-H. Epilepsy in children with a his- tory of febrile seizures. Korean J Pediatr. 2016;59(2):74-9
12. Ray BK, Bhattacharya S, Kundu TN, Saha SP, Das SK. Epidemiology of epilepsy - Indian perspective. J Indian Med Assoc 2002;100:322-6.
13. Mohammad R. Mohebbi, Reza Navipour, Mojdeh Seyed Kazemi*, HadiZamanian, FatemehKhamseh . Adult-onset epilepsy and history of childhood febrile seizures: A retrospective study. Neurol India. 2004 Dec; 52(4):463-5.
14. Abdullah I. Almojali,a Anwar E. Ahmed,b Muhammed Y. Baghac Prognostic factors for epilepsy following first febrile seizure in Saudi children. Ann Saudi Med 2017; 37(6): 449-454
15. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med 1987;316:493-8
16. Mohammad et al. Prevalence of epilepsy in Bangladesh: Results from a national household survey. Epilepsia Open. 2020;5:526–536
17. Scheffer I F, BerkovicS F. Generalized epilepsy with febrile seizure plus. A genetic disorder with heterogeneous clinical phenotype. Brain Dev. 1997; 120:479-90.
18. Singh R, Scheffer I E, Crossland K, Berkovic S F. Generalized Epilepsy with febrile seizure plus; A common childhood-onset genetic epilepsy syndrome. Ann Neurol. 1999; 45:75-81.
19. Chang BS, Lowenstein DH. Epilepsy. N Engl J Med. 2003; 349:1257-66
20. Hussain ME, Khan AFMAM, Islam MN, Mian MF, Azam MB, Chowdhury RN. Different Types of Epilepsy Based on Clinical and Electroencephalographic (EEG) Findings: Experience at Referral Neuroscience Hospital in Bangladesh. J Natl Inst Neurosci Bangladesh, 2017; 3(1): 3-6
21. Berg AT, Shinnar S. Unprovoked seizures in children with febrile seizures: Short-term outcome. Neurology.1996;47(2):562-8.
22. Hwang G, Kang HS, Park SY, Han KH, Kim SH. Predictors of unprovoked seizure after febrile seizure: short-term outcomes. Brain Dev. 2015;37(3):315-21.