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RESEARCH ARTICLE

RISK FACTORS FOR FEBRILE STATUS EPILEPTICUS: A CASE CONTROL STUDY

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ABSTRACT

Febrile seizures are the most common seizures in children below 5 years of age. If a febrile seizure persists more than 30 minutes, it is termed as febrile status. Risk factors for first febrile seizure are well established, but risk factors for febrile status are largely unknown. An observational, analytical study of case control design was done in the department of Pediatric medicine of R G Kar medical college, Kolkata to find out the risk factors. Children with febrile status epilepticus were grouped as cases and simple febrile seizure patients as control. The parents were interviewed based on the predesigned case-record proforma to elucidate the history. Clinical examination of the child and relevant investigations were also done. Categorical variables were compared in two groups with the help of Chi-square test and continuous variables with the help of t-test. Odds ratio with 95% confidence interval was calculated to determine the strength of association. It was seen that, children developed FSE in their first FS had lower temperatures (<102^0F), shorter duration of recognized fever prior to seizure (<12 hours) and younger age (<18 months) compared with children with simple FS. Preterm birth (<37 weeks), low birth weight (<2.5 kg) and history of developmental delay were pre and post natal factors responsible. Family history of FS and epilepsy in 1st degree relatives were indicative of a genetic background behind FSE. However these assumptions need further large multicentre studies for confirmation.

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INTRODUCTION

Febrile seizure is seizure that occur between the age group of 6 and 60 months with a temperature of 38˚C (100.4˚F) or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures[1] whereas febrile status epilepticus is a type of complex febrile seizure lasting more than 30 minute (Mohamad, 2016). Febrile seizures (FS) are the most common seizure type occurring in 2-5% of children under 5 years of age with a peak incidence in the 2nd year of life (Shinnar, 2003). Febrile status epilepticus (FSE) accounts for 5% of febrile seizures (Hersdorffer *et al.,* 2011) but 25% of all childhood status epilepticus and more than 70% of status epilepticus in the 2nd year of life (Shinnar *et al.,* 1997). While febrile seizures are generally considered benign, there is emerging evidence that in certain cases they can lead to chronic epilepsy. Febrile status epilepticus is a neurologic emergency and is associated with marked increased risk for developing epilepsy in population based studies (Annegers *et al.,* 1987). In order to prevent developing epilepsy in future, it is important to understand the basic mechanisms that trigger febrile seizures per se, the factors influencing its progression to develop febrile status epilepticus and also to look for the reasons for its occurrence only in pediatric population. Although risk factors for first febrile seizure are well established, (Bethune *et al.,* 1993; Huang *et al.,* 1999; Rantala *et al.,* 1995; Forsgren *et al.,* 1991) risk factors for febrile status epilepticus are largely unknown. Identifying the risk factors for febrile status epilepticus during the first febrile seizure may lead to better understanding, detection and efforts to prevent febrile status epilepticus. Moreover, not many studies have been conducted in this regard among Indian population. So the study is intended to identify the risk factors for febrile status epilepticus in children presenting with first febrile seizures.

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MATERIALS AND METHODS

This observational, analytical study of case control design was undertaken in the department of Pediatric medicine of R G Kar medical college, Kolkata during 2014-15. Approval was taken from institutional ethics committee before starting the study. During the study period, 158 patients were admitted with febrile seizure of which, 52 had febrile status epilepticus, 88 had simple febrile seizure and 18 had complex febrile seizure. We consider children with febrile status epilepticus as cases and simple febrile seizure patients as control. Patients with

complex febrile seizure were excluded from the group because febrile status epilepticus is now considered a type of complex febrile seizure (Waruiru, 2004) and risk factor identification is not possible between two similar groups. Informed consent of parents of each participating children was taken. The parents were interviewed based on the predesigned case-record proforma to elucidate the history. Clinical examination of the child and relevant investigations was done. All data were collected, compiled & subjected to statistical analysis with the help of SPSS software (version 20.0) and Medcalc (version 12.7.3). Microsoft word 2007 and Microsoft Excel 2007 were used to generate the tables, graphs etc. Categorical variables were compared in two groups with the help of Chi-square test and continuous variables with the help of t-test. All tests were 2-tailed. A p-value of <0.5 was considered statistically significant for all calculations. Odds ratio with 95% confidence interval was calculated to determine the strength of association.

RESULTS

140 children of 6 months- 5 years age group are included in our study. Of which 52 are cases who presented to us with febrile status epilepticus and rest are grouped as control presented with febrile seizure.

We grouped them arbitrarily to less or more than 18 months of age. It is seen that the result is statistically significant between the two group with p value 0.001. There was no statistically significant difference in terms of sex and religion between the groups. It is seen that, lower temperature (<1020F) has significant association with FSE than higher temperature (p value-0.000) and when seizure occurs within 12 hours of onset of fever it may succumb to FSE more than when seizure occurs after 12 hours of onset of fever (p value- 0.005). Prenatal factors (maternal illness during pregnancy, iron & folate supplementation, any other drug intake, smoking and alcohol intake) have not any significant association. Of perinatal factors though place and mode of delivery and history of SNCU admission have no association it is seen that preterm and low birth weight baby (<2.5 kg) babies are more prone to develop FSE (p value 0.000 in both) in future in comparison to their term and normal birth weight counterparts. Immunization status had no association. Children with developmental delay (p value 0.040), family history of febrile seizure in 1st degree relative (p value- 0.005) and family history of epilepsy in 1st degree relative (p value- 0.048) are more susceptible to develop FSE during their first febrile seizure (Table 1). The mean age of children with FSE is 18.13 months, earlier than the control group with mean age of 24.03 months (p value 0- 0.001).

Table 1. Distribution of study variables between two groups (cases and controls) and their statistical significance

Variables		Cases	Controls	χ 2 value	Df	P value
Age	<18 mths	30 (57.7%)	26 (29.6%)	10.790	1	0.001
	≥18 mths	22 (42.3%)	62 (70.4%)			
Sex	Male	30 (57.7%)	50 (56.8%)	0.01	1	0.92
	Female	22 (42.3%)	38 (43.2%)			
Religion	Hindu	23 (44.2%)	40 (45.5%)	0.02	1	0.888
	Muslim	29 (5.8%)	48 (54.5%)			
Temp ^{0}F	<102	27 (51.9%)	9 (10.2%)	29.748	1	0.000
	>102	25 (48.1%)	79 (89.8%)			
Duration of fever prior to seizure (in hrs)	<12	37 (71.1%)	41 (45.6%)	7.993	1	0.005
	≥12	15 (28.9%)	47 53.4%)			
Number of febrile episode in last 1 year	≤2	33 (63.5%)	53 (60.2%)	0.144	1	0.704
	>2	19 (36.5%)	35 (39.8%)			
Maternal illness during pregnancy	Yes	10 (19.2%)	16 (18.8%)	0.024	1	0.887
	No	42 (80.8%)	72 (81.2%)			
Iron and folate supplementation	Yes	34 (65.4%)	56 (63.6%)	0.044	1	0.835
	No	18 (34.6%)	32 (36.4%)			
Maternal drug intake during pregnancy	Yes	8 (15.4%)	15 (17.1%)	0.066	1	0.798
	No	44(84.6%)	73 (82.9%)			
Maternal smoking	Yes	1 (1.9%)	0 (0%)	1.074	1	0.192
	No	51 (98.1%)	88 (100%)			
Maternal alcohol intake	Yes	0 (0%)	0 (0%)	Data cannot be analyzed		
	No	52 (100%)	88 (100%)			
Place of delivery	Institutional	44 (84.7%)	74 (84.1%)	0.007	1	0.934
	Home	8 (15.3%)	14 (15.9%)			
Mode of delivery	Vaginal	37 (71.2%)	61 (69.3%)	0.052	1	0.819
	Cesarean	15 (28.8%)	27 (30.7%)			
Gestational age	Preterm	24 (46.2%)	12 (13.6%)	18.093	1	0.000
	Term	28 (53.8%)	76 (86.4%)			
Birth weight	<2.5 kg	31 (59.6%)	20 (22.7%)	19.205	1	0.000
	≥2.5 kg	21 (20.4%)	68 (77.3%)			
H/o SNCU admission	Yes	15(28.8%)	16 (18.2%)	2.156	1	0.142
	No	37 (71.2%)	72 (81.8%)			
h/o exclusive breast feeding	Yes	32 (61.5%)	61 (69.3%)	0.887	1	0.346
	No	20 (38.5%)	27 (30.7%)			
Immunized(as per date)	Yes	39 (75%)	68 (77.3%)	0.094	1	0.76
	No	13 (25%)	20 (22.7%)			
Vaccine received in last 48 hours	Yes	5 (9.6%)	6 (6.8%)	0.353	1	0.552
	No	47 (90.4%)	82 (93.2%)			
h/o developmental delay	Yes	12 (23.1%)	9 (10.2%)	4.233	1	0.040
	No	40 (76.9%)	79 (89.8%)			
f/h of febrile seizure in 1st degree relative	Yes	14 (26.9%)	8 (9.1%)	7.847	1	0.005
	No	38 (73.1%)	80 (90.9%)			
f/h of epilepsy in 1st degree relative	Yes	10 (19.2%)	7 (7.9%)	3.896	1	0.048
	No	42 (80.8%)	81(92.1%)			

Table 2. Comparison of mean of variables between two groups

Variables		Mean	SD	SE of mean	P value (t- test)
Age (in months)	Case	18.13	8.60	1.192	0.001
	Control	24.03	10.88	1.160	
Temp ^{0}F	Case	101.90	0.85	0.117	0.000
	Control	103.09	0.83	0.088	
Duration of fever prior to seizure (in hrs)	Case	8.81	5.31	0.736	0.000
	Control	12.42	5.04	0.537	
Number of febrile episode in last 1 year	Case	2.12	0.94	0.131	0.937
	Control	2.10	0.95	0.101	
Gestational age	Case	36.17	3.41	0.472	0.000
	Control	38.11	2.35	0.251	
Birth weight	Case	2.19	0.62	0.854	0.000
	Control	2.58	0.46	0.490	

Table 3. Odds ratio of factors with significant association with FSE

Factors		FSE No %	FS No %	Univariate OR (95% CI)	P value
Age	<18 months	30 (57.7%)	26 (29.6%)	3.3 (1,6,6.7)	0.001
	≥18 months	22 (42.3%)	62 (70.4%)	1.0 (referent)	
Temperature	< 1020F	22 (57.9%)	9 (10.2%)	9.5 (3.9, 22.8)	0.000
	≥1020F	25 (48.1%)	79 (89.8%)	1.0 (referent)	
Duration of recognized fever	<12 hours	37 (71.2%)	41 (45.6%)	2.8 (1.4, 5.9)	0.005
	≥12 hours	5 (28.8%)	47 (53.4%)	1.0 (referent)	
Gestational age	<37 weeks	24 (46.2%)	12 (13.6%)	5.4 (2.4, 12.3)	0.000
	≥37 weeks	48 (53.8%)	76 (86.4%)	1.0 (referent)	
Birth weight	<2.5 kg	31 (59.6%)	20 (22.7%)	5.0 (2.4,10.6)	0.000
	≥ 2.5 kg	21 (20.4%)	68 (77.3%)	1.0 (referent)	
Developmental delay	Yes	12 (23.1%)	9 (10.2%)	2.6 (1.0, 6.8)	0.040
	No	40 (76.9%)	79 (89.8%)	1.0 (referent)	
F/H of febrile seizure in 1st degree relative	Yes	14 (26.9%)	8 (9.1%)	3.7 (1.4, 9.5)	0.005
	No	38 (73.1%)	80 (90.9%)	1.0 (referent)	
F/H of epilepsy in 1st degree relative	Yes	10 (19.2%)	7 (7.9%)	1.7 (1.1, 2.7)	0.048
	No	42 (80.8%)	81 (92.1%)	1.0 (referent)	

Children with FSE develop the seizure in lower temperature range (101.90F). Differences in mean temperature between two groups is also statistically significant. Mean duration of recognized fever prior to seizure is 8.81 hours in FSE and 12.42 hours in FS. Mean gestational age at time of birth of children suffered from FSE is 36.17 weeks whereas it is 38.11 weeks in control group (the differences is statistically significant). Children with FSE was LBW baby (mean wt. 2.19 kg) compared to children with FS (mean wt. 2.58 kg). (Table 2)

DISCUSSION

The study variables are discussed here as per result and compared with similar studies. In our study, age <18 months at the time of 1st febrile seizure was significantly associated with FSE as compared to simple FS (P = 0.001, OR 3.3). The result is similar to study of Hesdorffer *et al.,* 1975 in which age < 18 months was significantly associated with FSE (P = 0.004, OR 2.7). Although most authors agree with the present conclusion that younger children are more severely affected, the critical age below which convulsions are more likely to be complicated has varied. Lennox *et al.,* 1949 and Doose *et al.,* 1966 suggest up to 12 months, Wallace *et al.,* 1975 up to 15 months, and Aicardi and Chevrie *et al.,* 1970 up to 18 months. In the present study, the mean age was 18.13 months for FSE and 24.03 months for simple FS (P = 0.001). This is slightly more than that found in the study by Hesdorffer *et al.,* 2013 in which mean age was 15 months for FSE and 19 months for simple FS (P = 0.003). Based on this result, there is a possibility that the mean age for 1st FS in Indian population is more than the Western population. In our study, although the percentage of male population was more than female population in both Case (57.7% v/s 42.3%) and Control group (56.8% v/s 43.2%), the distribution was not significant (P = 0.92). Similar result was seen by Wallace *et al.,* 1975 and Lennox Buchtal *et al.,* 1973 which showed no sex predilection for FSE. However few studies, like those by Hesdorffer *et al.,* 2013 and Taylor *et al.,* 1971 demonstrated female sex is more susceptible to FSE. These conflicting results need further large studies in this regard to arrive at a conclusion. In the present study, no statistically significant difference in distribution was noted among Case and Control group in terms of religion (P = 0.888). No such data is available in other studies.

Temperature <102˚F was significantly more associated with FSE compared to simple FS (P =0.000, OR 9.5) while the mean temperature was 101.9˚F in Case group and 103.09˚F in Control group (P = 0.000). The result is similar to the study by Hesdorffer *et al.,* 2013 where the mean temperature was 102.3 ˚F for FSE and 103.6 ˚F for simple FS (P=0.0001). Another study by Berg *et al.,* 1996 showed that a low fever at the time of the seizure was marginally associated with prolonged duration. This shows that lower temperature at the onset of seizure is associated with prolonged duration of seizure, suggesting a lower seizure threshold in children prone to FSE. Furthermore, shorter duration of recognized fever prior to seizure onset (<12 hours) was significantly more associated with FSE (P=0.005, OR 2.8). The mean duration of fever prior to seizure was 8.81 hrs for FSE and 12.42 hours for simple FS (P= 0.000) in our study. This again goes to suggest a lower seizure threshold in children prone to FSE. However in the study by Hesdorffer *et al.,* 2013 longer duration of recognized fever prior to FS (1-24 hrs) was associated with FSE (OR 2.2) while no association of fever duration with FSE was seen by Wallace *et al.,* 1975. Even though there are contradictory results in this regard, there are many studies like that by Shinnar *et al.,* 2002 and Berg *et al.,* 1996 showing that shorter

the duration of recognized fever, the higher the chance of recurrence and future epilepsy. Mean number of febrile illness in last 1year was 2.12 in Case group and 2.1 in Control group in our study, hence no significant association (P=0.937) was seen in terms of number of febrile illness in the preceding year. The result is similar to the study by Wallace *et al.,* 1975 (P=0.2). There are studies such as the one by Huang *et al.,* 20 suggesting that 4 or more number of febrile illness per year is an independent risk factor for FS (P=0.021) but no study till now has demonstrated its association with FSE. In our study, no significant association was found between maternal illness during pregnancy and FSE (P=0.877). Although it is associated with increased incidence of FS (Nelson and Ellenberg, 1990), its association with FSE has not been demonstrated. Iron and folic acid supplementation was not significantly associated with FSE (P= 0.835) in our study. No such data was available in similar studies for comparison. Only one mother had history of smoking in Case group while no such history was present in Control group, hence the distribution was insignificant (P= 0.192). Hesdorffer *et al.,* 2013 showed smoking during pregnancy is associated with increased risk of FSE (OR=3.4). Cultural difference between Western and Indian population could be responsible for the contradictory result. None of the mother in either Case or Control group had history of alcohol intake, hence no comment can be made in this regard. No significant association was seen between home delivery and FSE in our study (P=0.934). No such data is available in similar studies for comparison but studies like Forsgren *et al.,* 1991 suggest that perinatal factors are not associated with increased risk of FS, thus emphasizing more on prenatal factors. FSE was not significantly associated with either NVD or CS (P=0.819) in the present study. No such data is available in similar published study for comparison purpose. However studies regarding perinatal factors in febrile convulsion like Nelson *et al.,* 1990 Forsgren *et al.,* 1991 and Greenwood *et al.,* 1998 did not find any significant association between mode of delivery and FS. Preterm (<37 weeks) birth was significantly more associated with FSE compared to simple FS (P=0.000, OR 5.4) and the mean gestational age was 36.17 weeks in Case group and 38.11 weeks in Control group. The finding is similar to the one seen by Hesdorffer *et al.,* 2013 in which premature birth (<37 weeks) is associated with increased risk of FSE (OR =2.2). However study by Wallace *et al.,* 1975 did not show any association of perinatal factors with FSE. In the present study, low birth weight (<2.5 kg) is significantly associated with FSE (P =0.000, OR 5.0) and the mean birth weight in Case group is 2.19 kg while in Control group is 2.58 kg. While birth weight was not a variable in the study by Hesdorffer *et al.,* 2013 the association was found to be insignificant by Wallace *et al.,* 1975 Although the percentage of SNCU admission was more in Case group, it was not significant (P=0.142) in our study. No such data is available in the study by Hesdorffer *et al.,* 2013 and Wallace *et al.,* 1975.

There was no significant association between EBF for 6 months and FSE in the present study (P=0.346). No such data is available in similar studies for comparison. We did not find any significant association between immunization status of the child and FSE (P=0.76). No such data in similar studies are available for comparison. However a study by Cendes F *et al.,* 2011 showed that febrile seizures occurring after vaccination do not seem to be different from febrile seizures from other causes. Vaccine received within 48 hrs prior to seizure had no significant association with FSE in our study (P=0.552). Other similar studies have no such data for comparison. However a Cochrane review (Demicheli *et al.,* 2005) and a review of 530,000 children (Vestergaard *et al.,* 2004) receiving the MMR vaccine showed that the risk of febrile seizures increased only during the first two weeks after vaccination, was small (an additional one or two febrile seizures per 1,000 vaccinations), and was likely related to fever from the vaccine. There was a significant association between developmental delay and FSE in the present study (P=0.040, OR 2.6).The result is similar to the study by Hesdorffer *et al.,* 2011 in which FSE was significantly associated with developmental delay (P=0.010) while in the study by Wallace *et al.,* 1975, a similar association between developmental delay and FSE ($P < 0.05$) was seen in female population only. FS in 1st degree relative has significant association (P=0.005, OR3.7) with risk of developing FSE. This is suggestive of a genetic background of FSE. In the study by Hesdorffer *et al.,* 2013, no such association was seen by univariate analysis, but in a multivariate model, 1st degree family history of FS was associated with FSE. Wallace *et al.,* 1975 did not find any such association in the study. These conflicting results require large multicentric studies to arrive at a conclusion. In the present study, family history of epilepsy in 1st degree relative was found to have statistically significant association with FSE (P=0.048, OR 1.7). No such association was found by Hesdorffer *et al.,* 2013 and Wallace *et al.,* 1975. More studies are required to come to a conclusion.

Conclusion

These findings suggest that children prone to FSE in their first FS have a lower seizure threshold manifest in particular by lower temperatures (<102^{0}F), shorter duration of recognized fever prior to seizure (<12 hours) and younger age (<18 months) compared with children with simple FS. Preterm birth (<37 weeks) and low birth weight (<2.5 kg) suggests the role of prenatal factors and history of developmental delay of post natal factor as a risk factor. Family history of FS and epilepsy in 1st degree relatives are indicative of a genetic background in FSE. However these assumptions need further large multicentre studies for confirmation.

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