Received 30 December 2022 | Accepted 20 January 2023
DOI: http://doi.org/10.4038/sljon.v9i1.132

SLJoN

RESEARCH ARTICLE

Risk factors for development of febrile seizures in children admitted to Lady Ridgeway Hospital, Sri Lanka

Jithangi Wanigasinghe[1], Poorna A de Silva[1], Udara Dasanayake[1], Carukshi Arambepola[2]

[1]Department of Paediatrics, University of Colombo, Sri Lanka.

[2]Department of Community Medicine, University of Colombo, Sri Lanka.

Correspondence

Jithangi Wanigasinghe

Department of Paediatrics, University of Colombo, Sri Lanka.

E-mail: jithangi@pdt.cmb.ac.lk

Abstract

Background: Febrile seizures (FS) are reported more frequently in the Asian population. Identifying risk factors for the development of FS, would enable parents and health care providers to avoid any preventable factors. There is no data on risk factors for developing febrile seizures in Sri Lankan children.

Methods: An unmatched case-control study was performed at the premier children's hospital in the country over a 6-month period. Children aged 6 months to 6 years, who presented with FS (first ever or recurrence), confirmed by a paediatrician, were recruited for the study. The controls were children presenting with a febrile illness not complicated with seizures. History and examination were used to identify any underlying neurological disorder or developmental delay. Interviewer-administered questionnaire, clinic records and haematological investigations were used for risk factor evaluation. Risk of potential variables was assessed by calculating the odds ratio (OR).

Results: There were 74 cases and 67 controls. Their corresponding median ages were 28 (IQR 16) and 36 (IQR 48) months. Among cases, 62% presented with simple FS and all others with complex febrile seizures; 5.4% presented in status epilepticus. Thirty-four (50%) presented with their first ever seizure; in the balance it was a recurrence.

It was only the family history of febrile seizures (OR=6.27) and low axillary temperature at time of seizure (OR=2.21) that were found to be associated with a significant risk of development of febrile seizures in our patients.

Conclusion: This study described the demographics of FS and identified the risk factors for development of FS in Sri Lankan children.

KEYWORDS
Risk factors, South Asia

INTRODUCTION

A febrile seizure (FS) is defined as a seizure occurring in childhood after one month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures[1]. It is the most common form of childhood seizures, affecting 2-5% of children between six months to six years, with peak incidence at about 18 months[2]. Febrile seizures are considered benign and self-limiting; however, it is a terrifying event for most parents and is one of the most common causes of visits to the emergency room[3].

Febrile seizures are reported more frequently in the Asian population[4]; affecting 3.4-9.3% of Japanese children[5] and 5-10% of Indian children[6], in contrast to 2-5% of children reported from the United States and Western Europe. The highest prevalence of 14% is reported from Guam[7]. Variation in the prevalence is likely to be affected not only by the differences in case definition and ascertainment methods, but also by geographical variation of risk factors and population specific cultural factors[8]. Therefore, it is rational to hypothesize that risk factors may differ in different geographical settings.

There are several reported risk factors for developing a first FS. They vary across studies. Some include prior neuro-developmental abnormality, increased number of febrile illnesses, day-care attendance, temperature greater than 39.4°C, HHV-6 infection, maternal smoking and a first-degree family history of FS[9,10]. Pre- or peri-natal factors, such as low birth weight and preterm birth, are some other reported risk factors for a first FS[11]. Peak body temperature, underlying cause of fever, antenatal and natal complications, low serum calcium, low sodium, blood sugar and microcytic hypochromic anaemia have also been mentioned[12]. Some reports categorise them as definite risk factors and associated risk factors, based on the significance of each risk factor[13]. These are somewhat different from the risk factors described for recurrence of FS, which include early age of onset, lower temperature close to 38°C at the time of first convulsion, shorter duration (<1 hour) of fever before the seizure and family history of FS[8,14].

Identifying risk factors would enable health care providers to prioritise health services including preventive and curative measures to the vulnerable populations. In Sri Lanka, only very few studies have been performed on FS, and none were related to risk factor identification. This study attempted to describe the demographic variation of children admitted with FS and to identify the potential risk factors for their occurrence. Ethical approval was granted by the Ethics Review Committee of the Faculty of Medicine, University of Colombo.

METHODS

An unmatched case-control study was performed at the Lady Ridgeway Hospital, which is the largest children's hospital in South Asia with a bed capacity of over 900. It serves a wide variety of general and specialist services for children below 14 years of age. It provides neurology care in outpatient, clinic and ward settings by paediatricians and paediatric neurologists. In this study, cases comprised of children presenting with FS. They included those with simple and complex types and both first presentation and recurrence. The case definition was based on that derived from the International League Against Epilepsy (ILAE)[1]. The controls comprised of children presenting with febrile illness without a seizure. Children of the age group of 6 months to 6 years were selected to avoid the inclusion of any child with another cause for acute symptomatic seizures. Those diagnosed with epilepsy or neurological disorders predisposing to afebrile seizures or those with developmental delay were excluded.

The sample size was calculated as 67 in each group of cases and controls, to evaluate an expected risk of 29% for FS (odds ratio = 3.74) reported with first degree family history; at 95% confidence level with statistical power of 80%; and control to cases ratio of one[15]. Consecutive sampling was used to obtain this number from among those admitted to the hospital between 8.00 to 16.00 to facilitate assessment without delay.

The risk factors for FS were ascertained in both cases and controls using a 16-point check list developed following a detailed PubMed search for previous descriptions of risk factors. For this purpose, parent interview, neurological examination performed by the investigators and review of the past medical records and in-hospital medical records were utilised as study instruments. Family history was evaluated across three generations. In case of parents not being aware of any positive history, a follow-up telephone call after discharge was given to obtain accurate and complete family history. Axillary temperature at the time of seizure was taken from the hospital record of temperature at the emergency room at the time of admission. If this information was unavailable, the temperature recorded by parent/guardian up to 30 minutes prior to the onset of the seizure was considered. The degree of temperature was then dichotomized as low axillary temperature (if less than 102° F ahrenheit) and as high axillary temperature (if more than 102° F ahrenheit). Haemoglobin level and red cell indices (mean corpuscular volume, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration and the red cell distribution width) were used as indicators of iron deficiency anaemia. Serum ferritin, which is a better indicator, could not be used due to non-availability.

Data analysis

Data was analysed using Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive statistics included proportions for qualitative data; and mean and standard deviation (SD) or median and interquartile range (IQR) for quantitative data. Risk of each potential variable was assessed by calculating the odds ratio (OR) at 5% significance level in univariate analysis.

RESULTS

There were 74 cases and 67 controls recruited for the study (Table 1). The median ages of cases and controls were 28 months (IQR 16) and 36 months (IQR 48), indicating a significant difference (p=0.01). Gender and ethnic distribution were almost equal in the two groups.

Cases were between the ages of seven months to five years. Mean age at onset of FS was 18.0 months (SD=10.37). Sixty two percent presented with a simple febrile seizure; and 38% with a complex febrile seizure. Those who developed febrile status epilepticus (seizure lasting more than 30 minutes) comprised 5.4% of the group. Thirty-seven (50%) presented with a recurrence. There were 10 with focal seizures (13.5%); others experienced generalized seizures. The generalized seizures included atonic (4.1%), clonic (2.7%), tonic-clonic (58.1%) and tonic seizures (21.6%).

The risk factors that were analyzed included genetic background such as family history of FS and epilepsy and consanguinity; patient factors such as age at onset, mode of delivery, APGAR score, low birth weight, prematurity, neonatal intensive care unit (NICU) stay, height of axillary temperature and vaccination preceding admission; environmental influences such as day-care attendance; and maternal factors such as maternal smoking, maternal alcohol use, maternal illness and exclusive breast feeding. The ORs for each of these risk factors are given in Table 2. Univariate analysis identified only two of the multiple risk factors to be statistically significant. They were the presence of a family history of FS (OR=6.27) and axillary temperature less than 102° F (OR=2.21) recorded at the time of seizure or in its close proximity.

DISCUSSION

This study attempted to evaluate the risk factors for development of febrile seizures in Sri Lankan children admitted to a tertiary children's hospital. Family history of FS and low axillary temperature at time of seizure were the two risk factors identified as being strongly associated with risk of development of FS. Although, several other known risk factors revealed a higher risk, none of these were found to be significant among this cohort of Sri Lankan children. Day care attendance, considered a risk factor for development of FS in other studies was not found to be significant. This may be related to the low day-care attendance seen in our community. The role of alcohol consumption during pregnancy, maternal smoking, low APGAR score, recent vaccination and family history of epilepsy as risk factors could not be assessed. Univariate analysis could not be performed on these risk factors due to the low number or absence of patients in these categories.

The importance of identification of risk factors relates to understanding the role played by different factors to cause FS

TABLE 1 Basic characteristics of the cases (with febrile seizures) and controls (with febrile illness without convulsions) in the sample

Characteristic	Cases (n=74)	Controls (n=67)
Sex, No. (%)		
Males	23 (31.1)	32 (47.8)
Females	51 (68.9)	35 (52.2)
Age in months, Median (IQR)	28 (16)	36 (48)
Ethnicity, No. (%)		
Sinhala	52 (70.2)	55 (82.1)
Tamil	11 (14.9)	3 (4.5)
Muslim	11 (14.9)	9 (13.4)
Presence of illness, No. (%)		
Yes	42 (56.8)	55 (82.1)
No	32 (43.2)	12 (17.9)
Birth weight in kg, Mean (SD)	2.97 (0.51)	2.84 (0.59)

TABLE 2 **Risk factors for febrile seizures in children 6 months to 6 years**

Risk factor		No. (%) Cases	Controls	OR (95% CI)
Genetic				
Family history of FS	Yes	34 (45.9%)	8 (11.9%)	**6.27 (2.63, 14.94)**
	No (ref)	40 (54.1%)	59 (88.1%)	1.00
Consanguinity	Yes	5 (6.8%)	1 (1.5%)	4.78 (0.54, 41.67)
	No (ref)	69 (93.2%)	66 (98.5%)	1.00
Family history of epilepsy*	Yes	3 (4.1%)	0 (0.0%)	-
	No (ref)	71 (95.9%)	67 (100%)	
Patient factors				
Age at onset	< 12 months	5 (6.8%)	16 (23.9%)	0.23 (0.08, 0.67)
	12 months and above (ref)	69 (93.2%)	51 (76.1%)	1.00
Birth weight	Low (≤ 2.5 kg)	9 (12.2%)	13 (19.4%)	0.58 (0.23, 1.45)
	Normal (> 2.5 kg) (ref)	65 (87.8%)	54 (80.6%)	1.00
Prematurity	Premature (< 37 weeks)	3 (4.1%)	9 (13.4%)	0.27 (0.07, 1.05)
	No (ref)	71 (95.9%)	58 (86.6%)	1.00
Mode of delivery	Assisted	33 (44.6%)	21 (31.3%)	1.76 (0.88, 3.52)
	Normal (ref)	41 (55.4%)	46 (68.7%)	1.00
APGAR score		N=60**	N=47**	
at 10 minutes*	Normal	60 (100.0%)	47 (100.0%)	-
	Low (<6) (ref)	0 (0.0%)	0 (0.0%)	
NICU care	Yes	8 (10.8%)	13 (19.4%)	0.5 (0.19, 1.3)
	No (ref)	66 (89.2%)	54 (80.6%)	1.00
Iron deficiency anaemia	Yes	14 (18.9%)	7 (10.4%)	2.0 (0.75, 5.29)
	No (ref)	60 (81.1%)	60 (89.6%)	1.00
Maternal factors				
Maternal smoking*	Yes	0 (0.0%)	0 (0.0%)	-
during pregnancy	No (ref)	74 (100%)	67 (100.0%)	
Alcohol use during	Yes	1 (1.4%)	0 (0.0%)	-
pregnancy*	No (ref)	73 (100%)	67 (100%)	
Exclusive breast feeding	No	6 (8.1%)	6 (9.0%)	0.89 (0.28, 2.93)
	Yes (ref)	68 (91.9%)	61 (91.0%)	1.00
Maternal illness	Yes	20 (27.0%)	21 (31.3%)	0.81 (0.39, 1.68)
during pregnancy	No (ref)	54 (73.0%)	46 (68.7%)	1.00
Environmental factors				
Day-care attendance	No	68 (91.9%)	58 (86.6%)	1.76 (0.59, 5.24)
	Yes (ref)	6 (8.1%)	9 (13.4%)	1.00
Recent vaccination*	No	71 (95.9%)	67 (100%)	-
	Yes (ref)	3 (4.1%)	0 (0.0%)	
Axillary temperature	<102° F	45 (68.2%)	33 (49.3%)	**2.21 (1.09, 4.47)**
	≥ 102° F (ref)	21 (31.8%)	34 (50.7%)	1.00

* Univariate analysis was not performed as one cell contained zero values.

** Exact APGAR score was available only for this number.

in an individual child. Considering the multifactorial basis of pathogenesis, these variable factors may affect different children differently. Understanding which factor(s) is or are likely to be the reason for FS in a particular child will help to reason to parents the causality of this condition. This aids to understand which of these factors if at all are amenable to manipulation and thereby could be avoided to prevent future recurrence. It is also helpful to educate parents on factors that result in risk of recurrence in their child; thereby alleviating their unwarranted fears and stress.

Risk factors in FS are reported in relation to three different manifestations. They are risk factors for development of FS, as described in our study, risk factors for recurrence of FS and risk factors for development of recurrent febrile status epilepticus (FSE)[8]. Methodological differences contribute to variations in their interpretation where higher risk without statistical significance is sometimes considered as a potential risk factor in some studies. Berg et al. reported height of temperature and history of FS in a first or higher degree relative, similar to our findings, to be the only two risk factors identified from a multi-variate analysis in a study from Connecticut, USA[10]. Younger age at onset of first ever FS, presence of a lower temperature at time of seizure, a shorter duration between onset of fever and the seizure and family history of FS are associated with a significant risk of recurrence[16]. On the other hand, previous history of febrile status epilepticus and presence of any baseline Magnetic Resonance Imaging (MRI) abnormality as shown in the FEBSTAT study, significantly increase the risk of recurrent febrile status epilepticus[17]. Baseline MRI abnormalities being 4.3-fold commoner in those who experience focal or prolonged FS hints of underlying abnormal structure playing a role in the pathogenesis of these complex FS[18]. Contrary to this, the presence of electro-encephalography (EEG) abnormalities (temporal slowing and attenuation) in those with FSE was not associated with an increased risk of recurrence[19]. Performing EEG following FS, even in those with prolonged seizures or focal seizures, therefore helps little in risk evaluation.

Several studies from the region have raised a potential association between malnutrition and elemental metal deficiencies and FS[20]. However, significant variation in the findings across studies curtails understanding on their exact role. For example, while Thoman and colleagues found an association with sodium levels and risk of simple as well as complex FS than those presenting with afebrile seizures[21], other studies did not establish a significant association[22]. As a result, routine screening for electrolyte abnormalities is not recommended. Inability to perform sophisticated evaluation of nutritional status or incomplete evaluations may be a reason for this variability. We experienced similar difficulty in establishing iron deficiency anaemia as a definite risk factor among our children, possibly due to inability to use serum ferritin estimates, which is the best biochemical parameter.

In conclusion, this is the only study evaluating risk factors for development of FS in Sri Lankan children. This data will be helpful to both paediatricians and paediatric neurologists in educating parents regarding the pathogenesis of FS in their child. There are several limitations in the interpretation of some of the findings. This includes the evaluation of risk related to micronutrient deficiencies[23], of which only iron deficiency has been evaluated in this study. Due to logistical limitations, we were not able to test for any other elements such as zinc, magnesium and calcium, previously suggested to play a possible role in the pathogenesis of FS.

Funding

No funding was obtained for this study.

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