

Case control study of assessment of risk factors in febrile seizure at a tertiary hospital

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Abstract

Background: Febrile seizure is the most common form of seizures among all children's neurological problems; commonly affect children under 5 years of age. Febrile seizure is of multifactorial origin and different factors associated with its occurrences need to be identified. Early identification and management of risk factors can prevent the occurrence and recurrence of febrile seizures. Present study was focused on study of risk factors associated with febrile seizures in childhood at a tertiary health center. **Material and Methods:** Present study was a hospital based, prospective, case control study, conducted in department of Paediatrics and Adolescent Medicine, BPKIHS. Child Age >6 months to <5 years with febrile seizure were defined as cases. While apparently healthy siblings of cases, > 5 years age visiting paediatrics OPD were defined as controls. Clinical data was collected and analysed with software SPSS version 20. **Results:** During study period, 80 children with febrile seizure and 230 controls had fulfilled the inclusion criteria and were evaluated. There was no significant difference between cases and control regarding the gender. Minimum age of presentation was 6 month and maximum age of presentation was 60 month with median age of onset of febrile seizure was 18 months with IQ range of 10-24 months. Most of the cases of febrile seizure occurred at a temperature $\geq 102^{\circ}\text{F}$ (38.9°C). Most of the febrile seizure occurred within 24 hours of the onset of fever with 57.5% of cases occurring within 12 hours of fever onset. 63 cases (78.8%) had first febrile seizure and 17 cases (21.3%) had recurrent febrile seizure. Most common cause of fever among febrile seizures was upper respiratory tract infection (66%) followed by viral exanthematous fever (13%) and urinary tract infection (13%). There was no significant differences among cases and controls regarding place of delivery, h/o prolonged labor, and instrumental delivery with forceps or ventouse application. **Conclusion:** The commonest risk factor associated with febrile convulsion in this study were nonexclusive maternal breast feeding and family history of febrile seizure **Key Words:** febrile seizure, risk factors, nonexclusive maternal breast feeding, positive family history

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INTRODUCTION

Febrile seizure is the most common form of seizures among all children's neurological problems; commonly affect children under 5 years of age. The International league against epilepsy (ILAE) defines febrile seizure 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 or any metabolic encephalopathy, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures.¹ There are two types of febrile seizures: the simple and complex types. While the majority of febrile seizures are simple, incidence of complex febrile seizure among febrile seizures are 9-35%.^{2,3} Although Simple febrile seizures do not have an increased risk of mortality, Complex febrile seizures may have an approximately 2-fold long-term increase in mortality over the subsequent 2 years, probably secondary to coexisting pathology. Both types are concerning and distressful situation for a parent.⁴ In most patients, the height of the body temperature is considered to play a more important role in the pathogenesis of a febrile seizure than

the rapidity of the rise in the temperature.⁵ Many studies have also found that the risk may be increased by an underlying brain disorder. Premature birth, delayed discharge from the neonatal intensive care unit, and developmental delay are potential markers for suboptimal brain function, but there is conflicting evidence definitively linking these factors and Febrile Seizure.^{6,7} Febrile seizure do not cause decline in IQ, low academic performance, neurocognitive, inattention, or behavioural abnormalities.⁸ Febrile seizure is a common benign condition of multifactorial origin and different factors associated with its occurrences need to be identified. Early identification and management of risk factors can prevent the occurrence and recurrence of febrile seizures. Present study was focused on study of risk factors associated with febrile seizures in childhood at a tertiary health center.

MATERIAL AND METHODS

Present study was a hospital based Prospective, case control study, conducted in pediatric outpatient department, pediatric emergency unit and inpatient wards of department of Pediatrics and Adolescent Medicine, BPKIHS. Present study was of 1-year duration (February 20XX- January 20XX). Institutional Ethical Review Board (IERB) of B.P. Koirala institute of health sciences, Dharan approved present study and ethical clearance was provided.

Child Age >6 months to <5 years with febrile seizure were defined as cases.

Inclusion criteria

- Child with h/o Febrile seizure , 6 months- 5 years age, parent giving consent for participation.

Exclusion criteria

- Child with history of epilepsy or afebrile seizure
- Presence of focal neurological deficit
- Acute symptomatic seizures such as meningitis or CNS infection proven by lab reports and seizure apparently proven to be due to CNS insult other than febrile seizure
- Parents not willing for participation.

Apparently healthy siblings of cases, > 5 years age visiting pediatrics OPD were defined as controls.

Inclusion criteria

- Healthy children >5years, no history of febrile seizure and parents willing to participate

Exclusion criteria

- History of seizure disorder
- Major congenital malformations
- Developmental delay
- Genetic abnormality
- Parents not willing for participation.

Non purposive consecutive sampling method was done for selection of cases and Quota sampling was done for

selection of control. Cases and control matching with respect to age was not possible as there are chances of control presenting with febrile seizure during study period would have always been there. Parents/caregiver children selected for present study were interviewed and a complete description of seizure from the parent or from the eye witness was taken. Information such as age, gender, nature of illness, maternal history of smoking/alcohol consumption/use of recreational drugs, obstetric factors like gestational age at delivery, history of prolonged labor, instrumental delivery, birth weight, feeding practices such as exclusive MBF, top up feed, bottle feed family history, duration and level of fever, birth weight and immunization status was collected. Clinical examination for heart rate, respiratory rate, capillary refill time, temperature, pallor, icterus, clubbing, cyanosis, lymphadenopathy and edema was done. Anthropometric measurements such as weight (kg), length (cm), head circumference, mid upper arm circumference were taken. Head to toe examination and neurologic assessment was carried in detail to find the neurocutaneous marker and/or other features suggestive of different syndromes. Developmental assessment was done by detail history and examination for estimation of developmental age in each domain of gross motor, fine motor, social and language skills. The cases were investigated for fever and serum sodium and serum iron if ordered by treating pediatrician. Lumber puncture was done in indicated case and samples were sent in 2 vials with 8 drops in each for CSF routine examination, CSF biochemistry and CSF culture sensitivity. Venous sample was sent for complete blood count, serum sodium in controls. Relevant data was collected and entered Microsoft excel and analysed with software SPSS version 20. Statistical analysis was done using descriptive statistics. For comparing categorical variable among groups Chi square test and fisher’s exact test were used. A p value of <0.05 was considered significant.

RESULTS

During study period, 80 children with febrile seizure and 230 controls had fulfilled the inclusion criteria and were evaluated. Of 80 children with febrile seizure 44 cases (55%) were male with a M:F ratio of 1.2:1. Of 230 controls 120 (52.2%) were male and 110 (47.8%) were female with a M:F ratio of 1.1:1. There was no significant difference between cases and control regarding the gender.

Table 1: Gender distribution

Gender	Cases	Controls
Boys	44 (55%)	120 (52.2%)
Girls	36 (45%)	110 (47.8%)
Total	80	230

Minimum age of presentation was 6 month and maximum

age of presentation was 60 month with median age of presentation was 18 months with IQ range of 12- 30 months among cases. Median age of onset of febrile seizure was 18 months with IQ range of 10-24 months.

Table 2: Age distribution among cases and control

Age of onset of febrile seizure	Simple febrile seizure (n=58)	Complex febrile seizure (n=22)
Age<18 months	63.79%(n=37)	59.09%(n=13)
Age >18 months	36.21%(n=21)	40.91%(n=9)

Febrile seizure is more common among children residing in rural area (61.2%) compared to the urban residence (38.8%) but the differences were not statistically significant when compared to control group. Controls were

equal from rural area (50.4%) and urban residence (49.6%).

Table 3: Residence

Residence	Cases	Controls
Rural	49 (61.2%)	116 (50.4%)
Urban	31 (38.2%)	114 (49.6%)
Total	80	230

Most of the cases of febrile seizure occurred at a temperature $\geq 102^{\circ}\text{F}$ (38.9°C). Most of the febrile seizure occurred within 24 hours of the onset of fever with 57.5% of cases occurring within 12 hours of fever onset.

Table 4: Fever characteristics among febrile seizure

Temperature at presentation	Mean \pm SD - $100.51 \pm 0.693^{\circ}\text{F}$ Range= $100-102^{\circ}\text{F}$
Level of temperature at seizure onset	Mean \pm SD= $102.54 \pm 0.841^{\circ}\text{F}$ Range= $101-101^{\circ}\text{F}$ Median=12 hours
Gap between onset of fever and onset of seizure	IQ= $6-20$ hours Range= $1-72$ hours

Most common seizure type among febrile seizure at presentation was Generalized tonic clonic seizure (GTCS) in 80% cases. Of 80 cases 58(72.5%) had simple febrile seizure, 22(27.5%) had complex febrile seizure and 2(2.55%) had febrile status epilepticus. 63 cases (78.8%) had first febrile seizure and 17cases (21.3%) had recurrent febrile seizure. Most common cause of fever among febrile seizures was upper respiratory tract infection (66%) followed by viral exanthematous fever (13%) and urinary tract infection (13%).

Table 5: Causes of fever in febrile seizure cases

Cause of fever	No. of patients	Percentage
Upper respiratory tract infection (URTI)	53	66%
Viral exanthematous fever	10	13%
Urinary tract infection (UTI)	10	13%
Acute gastroenteritis (AGE)	4	5%
Pneumonia	3	4%

Of total cases one cases each were exposed to maternal smoking in-utero and drugs in form of oral and intravenous antibiotics and 19 cases had exposure to maternal alcohol in utero. There was no significant difference between two groups regarding the inutero exposure to risk factors.

Table 6: Antenatal exposure to risk factors among cases and control

Risk factors	Cases (n=80)	Control (n=230)	Odd's ratio	95% CI	P value
Smoking	1.3%(n=1)	0.9%(n=2)	0.693	0.062 7.747	1.00
Alcohol	23.8%(n=19)	17%(n=39)	0.988	0.963 1.012	0.258
Drugs IV and oral antibiotics	1.3%(n=1)	0%(n=0)	0.656	0.353 1.218	0.186

There was no significant differences among case and control regarding place of delivery, h/o prolonged labor, and instrumental delivery with forceps or ventouse application. Gestational age at delivery was 38.93 ± 1.73 weeks in case group compared to 39.04 ± 1.44 weeks in control group. ($P = 0.565$). Average birth weight was 2.77 ± 0.44 kg in case group compared to 2.75 ± 0.36 Kg in control group There was no significant difference between two groups regarding birth weight($p=0.697$). The incidence of low birth weight (<2500 g) among cases 17.5%(n=14) and control was 20.8%(n=48).

Table 7: Distribution of Birth history and perinatal insult among cases and control

Birth history	Cases(n=80)	Control (n=230)	Odd's ratio	95% CI	P value
Home delivery	52.5%(n=42)	58.3%(n=134)	1.263	0.758 2.105	0.432
Hospital delivery	47.5%(n=38)	41.7%(n=96)			

Prolonged labor	6.3%(n=5)	7%(n=6)	1.121	0.397	3.167	1.00
Instrumental delivery	8.8%(n=7)	16.1%(n=37)	1.999	0.853	4.685	0.136
Gestational age	38.93 ± 1.73 weeks	39.04 ± 1.44 weeks	0.577	- 0.504	0.275	0.565
Birth weight	2.77 ± 0.44 kg	2.75 ± 0.36 Kg	0.389	- 0.079	0.118	0.697

Proportion of babies exclusively breast fed for 6 month were significantly higher in control group whereas bottle fed babies were significantly higher in control group. Exclusively breast-fed children were among cases 56.3%(n=45) and control was 75.7%(n=174) and bottle-fed babies among cases 43.75%(n=35) and control 24.3%(n=56).

Table 8: Feeding status of cases and control

Breast Feeding	Cases (n=80)	Control (n=230)	adjusted odd's ratio	95%CI	P value
Exclusively breast fed	56.3%(n=45)	75.7%(n=174)	2.417	1.416-4.125	0.002
Bottle-fed babies	43.75%(n=35)	24.3%(n=56)	1.736	1.214-2.482	0.005

Statistically, a significant difference was found between two groups regarding the family history of febrile seizure but there was no significant difference between two groups regarding the family history of epilepsy

Table 9: Family history of febrile convulsion and epilepsy among cases among controls

Past history	Case (n=80)	Control (n=230)	Odd's ratio	P value
Family history of febrile seizure in first degree relative	13.8%(n=11)	0.9%(n=2)	5.750	0.000
Family history of febrile seizure in second degree relative	1.3%(n=1)	1.7%(n=4)		
Family history of epilepsy in second degree relative	1.3%(n=1)	2.6%(n=6)	0.719	0.767
Family history of epilepsy in third degree relative	2.5%(n=2)	2.6%(n=6)		

73 cases(91.3%) vs 218(94.8%) control were completely immunized as for age according to EPI only 1(1.3%) case vs 2(0.9%) control was non immunized. There was no significant difference between two groups regarding the immunization status (P=0.281). Median weight in case group was 10 Kg with IQ range of 8.25 – 12.27 Kg. Median height in case group was 78cm with IQ range of 73 – 88 cm. 20 cases (25%) had moderate wasting and 3 case (3.8%) had severe wasting and stunting. Mean hemoglobin in case group was 10.9±1.19 g/dl. 61cases (76.25%) were anemic out of which 46 cases (75.4%) had simple febrile seizure and 15 cases (24.6%) had complex febrile seizure.

Table 10: Anemia among cases and control

Type of seizure	Anemia 76.25% (n=61)	No anemia 23.75% (n=19)
Simple febrile seizure	75.4% (n=46)	63.2% (n=12)
complex febrile seizure	24.6% (n=15)	36.8% (n=7)

In the study, on Bivariate analysis, significant difference was found between cases and controls regarding the exclusive maternal breast feeding (p=0.001), bottle feeding (p=0.001) and family history of febrile seizure (p=0.000).

Table 11: Comparison of risk factor among children with febrile seizure (case group) and healthy group (control) group.

Risk factor	Case (n=80)	Control(n=230)	P value
Family history of febrile seizure	15%(n=12)	2.6%(n=6)	0
Exclusive maternal breast feed	56.2%(n=45)	75.7%(n=174)	0.002
Bottle feed	40%(n=32)	23%(n=53)	0.005
Residential setting (rural)	61.3% (n=49)	49.6% (n=114)	0.091
Instrumental delivery	8.8%(n=7)	16.1%(n=37)	0.136
Maternal alcohol	23.8%(n=19)	17%(n=39)	0.186
Maternal exposure to drug	1.2%(n=1)	0.0%(n=0)	0.258
Immunization status (non - immunized)	8.8%(n=7)	5,2%(n=12)	0.281
Home delivery	52.5%(n=42)	58.3%(n=134)	0.432
Family history of epilepsy	3.8%(n=3)	5.2%(n=12)	0.767
Maternal smoking	1.2%(n=1)	0.9%(n=2)	1
Prolonged labour	6.2%(n=5)	7.0%(n=16)	1

These variables were analyzed by binary logistic regression analysis. After binary logistic regression analysis, only family history of febrile seizure retained its statistical significance (p<0.001). Binary logistic regression analysis showed that family history of febrile seizure was associated with febrile seizure.

Table 12: Binary logistic regression analysis

Risk factors	Adjusted odds ratio	Odd's ratio		P value
		Lower	Upper	
Exclusive MBF	2.542	0.632	10.222	0.189
Bottle feed	0.935	0.227	3.851	0.926
Family history of febrile seizure	6.476	2.296	18.265	0.000

Similar risk factors were analyzed between simple and complex febrile seizure but none of the variable were significantly different between groups.

Table 13: Comparison of risk factors among simple febrile seizure and complex febrile seizure group

Risk factor	Simple febrile seizure (n=58)	complex febrile seizure (n=22)	P value
Hemoglobin	10.80±1.09	11.17±1.42	0.135
Level of temperature at seizure	102.52±0.80	102.59±0.959	0.19
Maternal smoking	0%(n=0)	4.5%(n=1)	0.275
Family H/O febrile seizure	1.7%(n=1)	0%(n=0)	0.306
Gestational age(weeks)	38.98±1.331	38.77±2.544	0.336
anemia	79.31%(n=46)	68.18%(n=15)	0.379
malnutrition	22.41%(n=13)	31.8%(n=7)	0.399
Birth weight(Kg)	2.77±0.425	2.78±0.502	0.461
Prolonged labour	5.17%(n=3)	9%(n=2)	0.612
Family history of epilepsy	3.4%(n=2)	4.5%(n=1)	0.641
Temperature	100.52±0.682	100.50±0.740	0.75
non immunized	8.6%(n=5)	9%(n=2)	0.786
Age of onset <18months	63.8%(n=37)	59.1%(n=13)	0.797
Maternal alcohol	24.13%(n=14)	22.72%(n=5)	1
Maternal drug	1.7%(n=1)	0%(n=0)	1
Exclusive MBF	56.89%(n=33)	54.54%(n=12)	1
Bottle feed	39.65%(n=23)	40.9%(n=9)	1

DISCUSSION

Febrile seizures are an age-dependent phenomenon with an underlying genetic susceptibility. Aside from age, the most commonly identified risk factors include high fever, viral infection, recent immunization, and a family history of febrile seizures. With the increasing age the incidence of febrile convulsion decreases which can be explained by the facts that the maturity and myelination progressively increases with age.⁹ Ojha *et al.* in Nepalese hospital-based study found that Males accounted for 62% and females 38%.¹⁰ Similar findings were noted in present study. Male predominance in febrile convulsions can be due to age-related sex differences in cerebral pruning and myelination which explains the mechanism of several developmental neuropsychiatric disorders.¹¹ We noted that the incidence of febrile seizure increases with temperature level. The reason behind this is that the threshold for seizure decreases with increase temperature.¹² The rate of increase in temperature has often been cited as an important factor in the provocation of a febrile seizure.¹³ Each additional degree of body temperature above 101°F (38.3°C) almost doubled the risk of FS (mOR 1.8, $p < 0.001$).¹⁴ The children FS had significantly higher temperatures at home (39.4 versus 38.8 °C, $p < 0.01$) and during the first 3 hospital days than controls. There was no difference in temperature

in children with simple or complex FS (39.4 versus 39.6 OC, $p = 0.36$).¹⁵ Recurrence of febrile convulsion was found in 21.3%. Shinnar *et al.* mentioned average recurrence rate 34.3%.¹⁶ Shrestha *et al.* found recurrent febrile seizures in 33%.¹⁷ True recurrence rate may be wrongly calculated due to not following up of the febrile seizure cases, many of which can throw seizure in subsequent febrile episodes. Berg *et al.*¹⁸ compared recurrences between children with fever lasting less than an hour, from one to 24 hours and more than 24 hours. The risk of recurrences decreased as the duration of fever prior to the first FS increased (RR 0.4, 95%CI 0.35- 0.66). In a matched case-control study to identify risk factors for first febrile seizures children having a febrile seizure had adjusted modified odds ratio (OR) of 4.8 for a positive family history of febrile seizure in first-degree relatives and 4.5 in second or higher-degree relatives compared with children with no history of febrile seizures.¹⁴ A positive family history of FS nearly triples the risk of recurrences, but there is no evident influence of unprovoked seizures in family members on the recurrence rate.¹⁹ The risk of having a sibling with FC was three times (95% confidence interval 1.3-6.2).²⁰ Both genetic and environmental mechanisms have been suggested for the susceptibility to an increased risk of the recurrence of

febrile seizures.¹⁴ Forsgren *et al.* found no association between febrile seizure and perinatal risk factors such as occurrence of chronic illnesses in mothers, parents age at birth, birth order, and factors occurring during delivery such as type of anesthesia, Occurrence of acute or elective cesarean section, use of vacuum extraction, mode of presentation, signs of fetal distress in amnion fluid, umbilical problems, abnormalities of fetal heart rate or duration of delivery.²¹ Similar results were noted in present study. Vestergaard *et al.* study on Prenatal Exposure to Cigarettes, Alcohol, and Coffee and the Risk for Febrile Seizures concludes that prenatal exposure to low to moderate levels of alcohol and coffee has no impact on the risk for febrile seizures, whereas a modest smoking effect cannot be ruled out.²² Another similar study of risk factors for febrile convulsion done by Vahidinia F *et al.* noted that children of mothers who both smoke and drink alcohol during pregnancy may have a higher risk for febrile convulsions.²⁴ There is a significant association between iron deficiency and febrile seizure in childhood. Children with febrile seizures were almost twice as likely to be iron deficient when compared with controls and proposed that iron deficiency is one of the risk factors for febrile seizure to be included along with others such as family history, rate of rise of fever, and specific viral illness.²⁴ While another study by Elham Bidabadi *et al.* suggest that iron deficiency anemia was less frequent among the cases with febrile convulsion, as compared to the controls, and there is not a protective effect of iron deficiency against febrile convulsions.²⁵ A similar study noted that the parameters such as gender, family history of febrile seizures, breast-feeding duration, and body temperature are among the risk factors in occurrence of the first febrile seizure and, thus, preventive measures in removing these risk factors could lead to a decrease in incidence of febrile seizures.⁹ While Offringa *et al.* concluded that the combined predictive value of age at onset, first-degree family history of seizures of any kind, nature of first seizure (single or multiple) and degree of fever at first seizure (more or less than 40oc) for both single and multiple recurrences is superior to that of single variables.²⁶ The cause of febrile seizure is multifactorial in origin and risk factors are also multiple. In present study, significant difference was found between cases and controls regarding the exclusive maternal breast feeding, bottle feeding and family history of febrile seizure. Present study was small sample size, observational study. We recommend larger, multicenter studies with sufficient sample size to draw conclusions regarding risk factors for febrile seizures.

CONCLUSION

The commonest risk factor associated with febrile convulsion in this study were nonexclusive maternal breast feeding and family history of febrile seizure. Exclusive

breast feeding for 6 months have protective role in febrile seizure, specially for those with positive family history. In children with positive family history of febrile seizures, supervision is required as they are highly susceptible to febrile seizure.

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