

Risk Factors for Febrile Seizures: A Matched Case Control Study

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ABSTRACT:

BACKGROUND:

A matched case control study was conducted over 6 months period from the 1st of November 1999 to 30th of April 2000 at the maternity and children hospital in Ramadi city with the aim of determining the risk factors that might lead to development of febrile seizures.

METHODS:

One hundred patients with febrile seizures admitted to the causality department, aged 6-60 months were matched with another one hundred child having fever but without seizure with the same age range, attending the same hospital during the same period.

RESULTS:

The mean age and standard deviation for cases was 25.8±15.19 months and for control was 29.9 ± 18.5 months .sixty four percent has febrile seizure for the first time and 36 %had recurrent febrile seizures. The mean age and standard deviation for the first FSs was 23.54± 12.8 months and for recurrent FSs was 29.83 ± 12.5 months. This was statistically not significant. The majority of the cases were between 12 -24 months with a peak at the age of 18 -19 months. Respiratory infections were not found to be a risk factor for FSs when compared with control.

CONCLUSION:

Male sex, degree of temperature on admission, presence of family history or epilepsy, developmental delay, anemia and admission to neonatal care unite were found to a significant risk factor for occurrence of febrile seizures. Patients are susceptible to develop another attack of seizure at a lower temperature after their first attack.

KEY WORDS: Febrile, Risk factors, Ramadi, Seizures

INTRODUCTION:

Febrile seizures (FSs) are benign convulsions that occur in infants or small children and are brought on by fever without evidence of meningitis or encephalitis ⁽¹⁾. It is the most common type of seizures and occurs in 2-4% of all children ⁽²⁾. In spite of its high prevalence, little is known about the etiology ⁽¹⁾ and many risk factors had been suggested ⁽³⁻¹³⁾. In a population study in south Taiwan, Huang found the presence of FSs in the siblings and the numbers of fever episodes per year were the independent and significant predictors of FSs for an individual case ⁽³⁾. Doose found that seizure incidence in offspring of individual with a history of FSs was 10% and offspring of females with affected parents were at an increased risk ⁽⁴⁾. In large families, the FSs susceptibility trait is inherited as autosomal dominant pattern with reduced penetrance, in other families; inheritance appears to be multifactorial ⁽⁵⁾.

A study from china confirmed the observation that familial factors are an important predisposing characteristic for febrile seizure ⁽⁶⁾. A higher percentage of developmental delay was found in cases when compared with control in the study of Huang ⁽³⁾. Another matched case control study from Italy found a significant increase in the risk of FSs associated with iron deficiency anemia in children below 2 years of age ⁽⁷⁾. A community based case control study in Sweden found no significant pre or perinatal risk factors for the development of febrile seizures ⁽⁸⁾. A similar study from United Kingdom confirmed this result ⁽⁹⁾. Other studies have reported a possible immunological derangement in the cytokines and interferon axis in FSs that may correlate with pathogenesis of FSs or at the fever ⁽¹⁰⁻¹²⁾. Many studies have also found that the risk may be increased by underlying brain disorders ⁽¹³⁾. Premature birth, delayed discharged from the neonatal intensive care unite, zinc deficiency and immunoglobulin deficiency are other debatable risk factors for developing FSs ^(2, 13-18).

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The aim of this study was to determine the possible risk factors for FSs among children attending maternity and children hospital in Ramadi city, west of Iraq.

PATIENTS AND METHODS:

A matched case control study was conducted during six months period from 1st of November 1999 to 30th of April 2000. All children admitted to the casualty department of maternity and children hospital in Ramadi city, with a diagnosis of FSs were enrolled as cases. For the purpose of this study, the case definition of a FS was a convulsive seizure in infants and children, aged between 6 months and 6 years, in association with fever 38°C or higher but without evidence of any definitive causative disease, such as CNS infections and metabolic disorders.

They were matched with controls by the same age range, who having fever but without seizure or past history of any type of seizure, admitted to the causality during the same period.

Patients with neurological disorder and those with CNS infection were excluded from both cases and control. Data were collected regarding socio-demographic characteristic, child's illness, neonatal history, developmental milestone and family history of FSs or epilepsy. Weight and height were recorded and full neurological examination was done and axillary temperature was taken for all patients at the time of admission. Hematocrit was done for all patients and PCV values below 33% were considered anemic according to WHO definition⁽¹⁹⁾.

Statistical analysis for collecting data was performed using the computer facility of Epi Info version 6 soft packages. Data were presented in frequency, percentage, mean, standard deviation and odd ratio. The odd ratio is a measurement of risk of a certain factors with its 95% confidence interval for the accurate range of risk. Student test (t-test) and chi square test was used for the significant testing with P value < 0.05 as the level of significance.

RESULTS:

During the study period , a total of 100 patients with FSs were identified and were matched to 100 control febrile patients without seizure with the same age range, who admitted the same hospital during the same period of time.

Table 1 shows the characteristics of the study groups. The mean age and standard deviation for cases was

25.8±15.19 months and for control was 29.9 ± 18.5 months. This was statistically not significant (P value > 0.05). Sixty four percent of cases had FSs for the first time and 36% had recurrent FSs.

The mean age and standard deviation for the first FSs was 23.54± 12.8 months and for recurrent FSs was 29.83 ± 12.5 months. This was statistically not significant (p value > 0.05). The majority of the cases were between 12 -24 months with a peak at the age of 18 -19 months. Of the characteristics studied, only the mean of temperature found to have high statistical significant difference between cases and control (p value = 0.0001).

Furthermore, cases with recurrent FSs have statistically significant lower temperature than those with first febrile seizure (p value = 0.0001) table 1. Table 2 gives risk factors for FSs.

In cases, male account for 64%, and female for 36% (male to female ratio 1.7: 1) while in control, there were 56% males and 44% females (male to female ratio 1.2: 1). Male found to be at risk for developing FSs (OR=1.4, 95% CI: 0.8- 2.5, p value = 0.05). Regarding the cause of fever, respiratory infections were not found to be a risk factor for FSs when compared with control (OR=1.35, 95% CI: 0.73-2.52, p value=0.304). Thirty three percent of cases had positive family history of FSs compared to 13% of control and this found to be a strong risk factor for febrile seizure (OR = 3.3 , 95% CI : 1.54 – 7.34 , p value 0.0008). In addition, 17% of cases compared to 7% of control had positive family history of epilepsy, this also found to be a risk factor for FSs (OR = 2.72, 95% CI: 1.9 – 8.12, p value = 0.029).

Also the developmental delay was found to be a risk factors for FSs as it present in 21% of cases compared to 8% of control (OR = 3.06, 95% CI: 1.21 – 8.4, p value = 0.009). Forty seven of cases were anemic compared to 25% of control and this found to be a risk factor for FSs (OR = 2.66, 95% CI: 1.4 – 5.08, p value = 0.001). Table 3 presents the perinatal risk factors for the development of FSs.

only the neonatal admission to neonatal care unit had statistical significance (OR = 2.35, 95% CI: 1.45 – 7.85, p value < 0.05) while Gestational age and neonatal condition after delivery were not found to be of statistical significance (p value > 0.05).

Table 1: characteristic of study group

Variable	Case no=100		Control no=100		T test	P value
	mean	SD	Mean	SD		
Age (months)	25.80	15.95	29.99	18.50	1.715	0.088
Age of the first FS No=64	23.54	12.8				>0.05
Age of the recurrent FS No=36	29.83	12.5				
Height(cm)	82.04	14.09	84.93	14.44	1.407	0.161
Weight(Kg)	12.35	4.663	13.45	5.174	1.524	0.129
Temp on admission	39.2	0.7	38.90	0.49		0.0001
Temp of first FS No=64	39.75	0.1				0.0001
Temp of recurrent FS No =36	38.24	0.45				

Table 2: Risk factor for febrile seizure

Risk factor	Case no=100		Control no=100		Odd ratio	95% Confidence interval	P value
	No	%	No	%			
Sex					1.4	0.8-2.5	0.05
• male	64	64	56	56			
• female	36	36	44	44			
Cause of fever					1.35	0.73-2.52	0.304
• respiratory	67	67	60	60			
• other causes	33	33	40	40			
Family history					3.3	1.54-7.34	0.0008
• febrile seizure	33	33	13	13			
• epilepsy	17	17	7	7	2.72	1.9-8.12	0.029
Development					3.06	1.21-8.4	0.009
• delayed	21	21	8	8			
• normal	79	79	92	92			
PCV					2.66	1.4-5.08	0.001
• anemic	47	47	25	25			
• normal	53	53	75	75			

Table 3: perinatal risk factors

Variable	Case no=100		Control no=100		Odd ratio	95% Confidence interval	P value
	No	%	No	%			
Gestational age							
• pre term	13	13	9	9	1.51	0.56-4.22	0.366
• full term	87	87	91	91			
Neonatal condition							
• cry immediately	82	82	89	89	1.78	0.74-4.42	0.160
• delayed cry	18	18	11	11			
Admission to neonatal care unit	26	26	13	13	2.35	1.45-7.85	< 0.05

DISCUSSION:

In the present study, the majority of cases of FSs occur in the second year of life, peaking at 18-19 months. This is in agreement with the results of other studies (20-22). FSs are age dependent and this age should be regarded as critical for developing FSs.

A unique age specificity of the maturing brain's sensitivity to fever due to enhanced neuronal excitability during the normal brain maturation had been suggested (13). The mean age for those with first febrile seizure was 23.5 months; this figure is similar to that found by Ploch of 22.5 months (23), but a study from Saudi Arabia report lower figure at 17.2 months (24). Another study from United Arab Emirates, revealed even a lower figure of 15.1 months (25).

This difference can be attributed to the lower age range taken by these studies (6-36 months).

The younger the child at the first FS, the more likely is recurrence (14, 23, and 26). Males account for 64% of cases with a male to female ratio of 1.7:1.

The male sex predominant is well documented in almost all series (27-31). There was no satisfactory explanation for this sex predominant (32).

Our study reveals that children with recurrent febrile seizure have a lower temperature at presentation than those with first febrile seizure (table 1). This result is in agreement with that of AL-Suweidi study (25). However, AL-Radhi in his study found a lower temperature at first febrile seizure is a risk factor not only for recurrent FSs but also for multiple convulsions and epilepsy (33). Thirty three percent of our cases were found to have family history of FSs and when compared with controls were found to be of statistical significance (p value=0.0008). This finding is in agreement with those studies that

showed strong evidence of a positive family history as a risk factor for febrile seizure (4, 5, 13, and 14).

Our figure is similar to that of AL -Eissa study (37%) (24), but higher than that of AL-Suweidi et al (21.4%) (25) and Berg et al (25%) (34), the reason for this difference is probably due to limitation of family history to the first degree of relatives in these studies. Furthermore, a family history of epilepsy was also found to be a risk factor for FSs (p value 0.029).

This is similar to the result of Fernandez et al (35) who revealed that the existence of family history of FSs or epilepsy increases the risk of recurrent FSs.

AL-Eissa in his study found that history of FSs and epilepsy in parent or siblings was marginally more common among children with complex febrile seizure than those with simple FSs (24).

Such association was not seen by another study (36). Genetic origin of FSs had been suggested by many studies are known to aggregate in families.

In some families, polygenic etiology is suggested and in other autosomal dominant inheritance pattern is observed (4, 37).

In the present study, delayed development milestone prior to the onset of first FSs were found to be a risk factor, a similar result was obtained by Huang et al and AL-Suweidi et al (3, 25). Developmental delay is one of the potential markers for suboptimal brain function, but there is conflicting evidence definitively linking this factor to FSs (13).

In our study , respiratory infections as a cause of fever were not found to be a risk factor for FSs as it is account for similar proportion of both cases and controls, 67% and 60% respectively (P value=0.304) table 2. This result differs from that of AL-Eissa and AL-Suweidi studies (24, 25) which found respiratory infections to be a risk factor. The explanation of this

difference is probably because most of the time of our study falls in cold season where respiratory infections account for the majority of admission to the hospital. Lewis et al in 1997 found that 90% of cases of FSs were due to disseminated viral infection of upper respiratory tract⁽³⁸⁾. In other study from Japan, approximately 90% of patients with FSs had upper and lower respiratory tract infection and exanthema subitum, and 20% of them was due to HHV-6 infection. Authors conclude that HHV-6 infection should be considered when encountering children under the age of one year with a first FS⁽³⁹⁾. A considerable number of children in our study were anemic, and when compared with control, anemia was found to be a significant risk factor (p value 0.001). The association between iron deficiency anemia and FSs was studied by many authors; some of them confirm this association^(40, 41) and the others conclude that the risk of FSs occurrence in anemic children seems to be less common than in children who do not suffer from anemia⁽⁴²⁾. In a well designed case control study from Italy, 30% of cases, aged 6-24 months, were found to have iron deficiency anemia compared to 12% of population control. The author suggests that fever can worsen the negative effect of anemia or iron deficiency on the brain and a seizure occurs as a consequence⁽⁷⁾. Our study differs from Italian one, in that we found the anemia as a risk factor in the whole age range of FSs (6-60 months). A prospective case control study is required to confirm the iron deficiency cause of anemia in our patients.

Neither the gestation age nor neonatal conditions after delivery were found to be a risk factor for FSs. This finding is in agreement with study by Greenwood et al⁽⁹⁾ but contrast with AL – Sweidi et al study which found prematurity as a risk factor for febrile seizure⁽²⁵⁾. However, admission to the neonatal care unit was found to be a risk factor for febrile seizure. Many studies have found that the risk may be increased by delayed discharge from neonatal intensive care unite (more than 30 days)⁽¹³⁾.

In a community based case control study from Sweden, premature birth and bilirubinemia greater than 200 mmol/L were more common in cases⁽⁸⁾.

The main limitation of this study was being a hospital based. However, from the results of this study we can conclude the major risk factors for FSs in our patients are male sex, positive family history of FSs or epilepsy, delayed developmental mile stone, admission to neonatal care unite and anemia. A

future study to confirm iron deficiency cause of anemia is needed.

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