

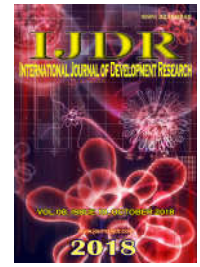


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RISK FACTORS OF FEBRILE CONVULSION AMONG CHILDREN UNDER 5 YEARS, INTERVENTIONAL STUDY IN MOSUL CITY

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ABSTRACT

Background: Febrile convulsion is the most common convulsive disorder in childhood. It is defined as a seizure occurring in a child aged 3 months to 5 years associated with fever but without evidence of intracranial infection or defined cause of their convulsion.

Aim of study: to identify the risk factors of febrile convulsion among children admitted to pediatrics hospitals in Mosul city.

Patient (material) and method: a case-control hospital based study. The present study was conducted in the three main pediatric hospitals in Mosul city: Ibn Seena, Ibn Al-Atheer, and AL-Khansa, teaching hospitals. It has been planned to collect data during six months period from 1st of January -30th of June 2008. 150 children who have been diagnosed by specialist pediatrician to have febrile convulsion (cases) with another 150 children (controls) who suffered from any disease other than FC with no previous history of febrile convulsion. Especially design questionnaire form has been prepared; these questionnaires were filled by interview with caregiver of both cases and controls. Chi square test (χ^2) for contingency tables to find the significance of the statistical association between cases and controls and the risk factor of interest was used. The 95% confidence interval (CI) for the odd ratio was calculated using Mistiness test based approach. P- Value considered significant if it is ≤ 0.05 for the entire study.

Result: The present study showed that Gastroenteritis constituted a major cause of fever among cases of FC and 74.6% of cases were simple febrile convulsion, male affected more than female. Regarding risk factors of FC, the study demonstrates the following significant predictors of development of febrile convulsion: Regarding the age group demonstrates significant association between age and occurrence of FC. A child whose age between 3months to <1 year is two times more prone to develop FC than those between 1-3 year and older. Family history of febrile convulsion among first-degree relatives, father smoking during pregnancy and low birth weight baby.

Conclusion: The following conclusions were obtained from the present study.

1-Gastroenteritis constituted a major cause of fever among cases of FC.

2-Three quarters (74.7%) of cases were simple febrile convulsion.

3-The following factors were emerged as a risk predictors of development of FC among study sample: Family history of febrile convulsion among first-degree relatives, father smoking during pregnancy and low birth weight baby.

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INTRODUCTION

Overview of epidemiology of febrile convulsion: Febrile convulsion (FC) is the most common convulsive disorder in childhood. They were recognized as distinct from other seizures in the mid-19th century, with the introduction of the thermometer at the end of the 1800s, fever was understood to be the primary factor producing the convulsion; and at that

time, treatment was redirected to the underlying causes of fever rather than the symptoms of a seizure. Many parents who had witnessed a child first convulsion think that their child is going to die or is already died. Intense parental anxiety and fear for recurrence is observed when febrile seizures are emotionally traumatic for parents, families may subsequently report persistent fear of fever and of febrile seizures with associated altered parental behavior and disruption of family

routines. Each year, about 150,000 children and adolescents in the United States will come to medical attention for evaluation of a newly occurring seizure disorder of some type. Between 2% and 4% of all children in Europe and United States experience at least one convulsion associated with febrile illness before the age of 5 years. The cumulative incidence of FC among children is variable from about 1% in China to more than 8% in Japan and 5-10% in India. It has been stated that between 2% and 4% of children will have FC and about 4% of cases arise before 6 months old, 90% between 6 months and 3 years and the other 6% over 3 years. Thirty percent will have another FC but less than 10% have more than three. FC is more likely to occur if there is family history of such disorder especially in first degree relative.

Definition and causation: The National Institutes of Health (NIH) has defined FC is a seizure occurring in a child aged 3 months to 5 years associated with fever but without evidence of intracranial infection or defined cause of their convulsion. The symptoms of FC include some or all of the following.

- Loss of consciousness.
- Twitching or jerking of arms and legs.
- Breathing difficulty.
- Foaming at the mouth (frothy secretion).
- Skin becomes pale or bluish in color.
- Eye rolling, only the white of eyes is visible.
- Involuntary urination or defecation.
- Confusion, sleepiness, or irritability after the seizure.

The generally accepted criteria for febrile seizures include.

- A convulsion associated with an elevated temperature greater than 38°C.
- A child between three to sixty months of age.
- No central nervous system infection or inflammation.
- No acute systemic metabolic abnormality that may produce convulsions.
- No history of previous a febrile seizures.

Etiology: Three features interact to bring on a febrile seizure: immature brain, fever and genetic predisposition.

Classification of febrile convulsion:

Simple febrile convulsion: It is common type of FC constitutes about 70% of cases characterized by isolated convulsion, generalized (jerking both of arms and legs), it has a duration of fit less than 15 minutes tonic- clonic seizure does not recur during the febrile episode, this type shows good prognosis and does not left any neurological deficit in the future of the child.

Complex febrile convulsion: It is less common type constitutes 25-30% of cases characterized by focal features; it has a duration of a more than 15 minutes, more than one seizure during the febrile episode, this type shows bad prognosis than simple type. Complex febrile convulsion had been shown to be related to subsequent epilepsy. In addition, earlier studies carried the notion that complex febrile convulsion was also associated with increased mortality and long-term neurological deficits.

PATIENTS AND METHODS

Study setting: The present study was conducted in the three main pediatric hospitals in Mosul city; these are Ibn Seena, Ibn Al-Atheer, and AL-Khansa, teaching hospitals. These hospitals receives cases either directly from their causality unit or referred cases from primary health care centers (PHCCS) which are distributed throughout Mosul city.

Study design: To achieve the aim of the present study, a hospital based case- control study design was chosen (Figure 2.1).

Study period: It has been planned to collect data during six months period from 1st of January -30th of June 2008.

Study sample: The study was conducted upon 150 cases and 150 controls who have been collected over period of six months.

Pilot Study: Exploratory visits have been carried out to the three main hospitals from which the study sample is decided to be taken. The directors of those hospitals were interviewed and informed about the objectives of the present study.

Pilot study was done over a period of three weeks during which 21 cases of FC were collected every other day from the three hospitals.....

The main objectives of pilot study were to:

- To know completeness and suitability of the questionnaire form and to look for the required modification.
- Determine kinds of difficulties that may arise during data collection period.
- Estimate the approximate sample size and time needed for filling in each questionnaire form.
- Test the cases and controls relative cooperation.

The main feed back points are:

1. Some questions are not clear to the parents or (care giver of the child) so the investigator discussed these questions in simple way
2. The relatives of child could not be interviewed before establishing the diagnosis and look for investigation to exclude metabolic convulsion and central nervous infection.
3. There are some sensitive questions to the mother like history of smoking during pregnancy, so the investigator try to explain to the mother relation between this habit during pregnancy and developing of FC, and this need extra time to obtain information.

The maximum number of cases that can be collected reached 6-8 cases per a week. So the sample sizes that can be obtained during 6 months period reach 150-200 cases. The time needed for filling in each questionnaire form was approximately 30 minutes.

Data analysis: Computer feeding tabulation and statistical analysis were carried out using Pentium IV by using Stat Exact under window and Minitab under window program. Table 2.2

show the method of tabulation of cases and controls in order to calculate the odd ratio (OR).

Risk factor	Cases of convulsion	Controls without convulsion
Present	a	B
Absent	c	D

Because of the case – control nature of the study, the incidence cannot be derived here for those exposed and not exposed so calculation of OR give a close approximation to this relative risk in this situation. $OR=ad / bc$ Chi esquire test (χ^2) for contingency tables to find the significance of the statistical association between cases and controls and the risk factor of interest was used . The 95% confidence interval (CI) for the odd ratio was calculated using Mistiness test based approach. P- Value considered significant if it is ≤ 0.05 for the entire study.

Result: 3.1 Description of febrile convulsion cases

Table (3.1) shows frequency distribution of both cases and controls across Ibn-Seena, Ibn-Altheer and Al-Khansa hospitals. Almost one half (46.0%) of study sample were taken from Ibn Seena hospital.

Table 3.1. Distribution of study Cases according to the study sites

Hospitals	Cases		Control	
	No.	%	No.	%
Ibn Seena	69	46.0	69	46.0
Ibn Al-Atheer	42	28.0	42	28.0
Al-Khansa	39	26.0	39	26.0
Total	150	100%	150	100%

Figure (3.1) shows that 74.7% of cases are simple febrile convulsion and 25.3% are complex febrile convulsion.

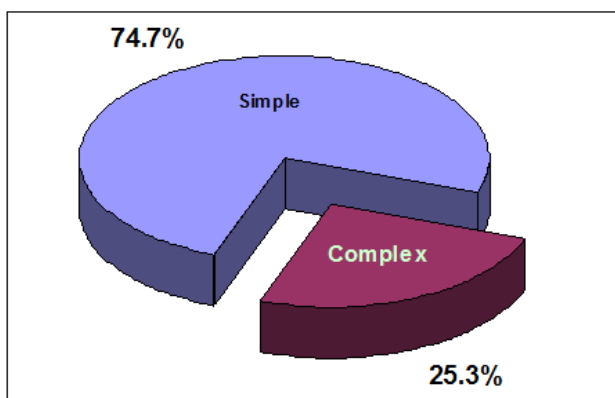


Figure 3.1. Distribution of FC cases according to type of FC

Regarding causes of fever among FC cases figure (3.2) demonstrates that gastroenteritis constitutes 39.3% while only 2% occur post vaccination (1.3% after measles vaccination and 0.7% after DPT vaccination).

Socio Demographic characteristics of study population

Table (3.2) illustrates that two third (62.0%) of cases and more than one halve (59.3%) of controls are lying in the age group 3 months - <1year. It depicts that male is the predominant gender in cases where it constitutes about 64.0% of cases in comparison to 52.0% in controls. The same table demonstrates

that, 78.7% of cases of FC living in urban area compared to 87.3% of controls.

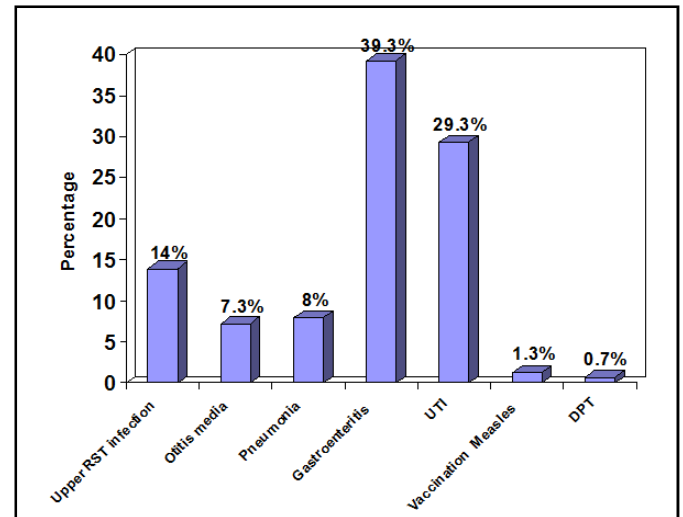


Figure 3.2. Causes of fever among FC cases

Table 3.2. Characteristics of study population

Age groups (in year)	Cases N=150		Controls N=150	
	NO	%	NO	%
3 month- <1	93	62.0	89	59.3
1-<3	37	24.7	25	16.7
3-5	20	13.3	36	24.0
Gender				
Male	96	64.0	78	52.0
Female	54	36	72	48.0
Residence				
Rural	32	21.3	19	12.7
Urban	118	78.7	131	87.3

Demographic characteristic of study population: Regarding the age group Table (3.3) demonstrates significant association between age and occurrence of FC. A child whose age between 3months to <1 year is two times more prone to develop FC than those between 1-3 year and older (P=0.01, OR=2.62, 95%CI=1.26-5.61) The same table clarifies significant association between male gender and occurrence of FC which appeared from P value (=0.003)and (OR=1.64, 95% CI=1.03- 2.06). Residence also shows a significant casual association between rural residency and occurrence of FC (P=0.046, OR=1.87, 95% CI= 1.0-3.84).

Family history of FC: The association between family history of FC among first degree relatives(siblings and / or parents) and development of this event is shown in Table (3.4) it clarifies a highly significant association between occurrence of FC and this variable, (P=0.001) . Odd ratio reveals that those with positive family history of FC among first degree relatives had 21 times risk to develop FC than those without (OR=21.67, 95%CI= 10.99-42.74). While no significant association is shown between family history of FC among second degree relatives (grand parents, uncles / aunts or cousins) and development of FC.

Parental smoking: Regarding mother smoking during pregnancy Table (3.5) shows no significant association between maternal smoking and occurrence of FC. While in the same table father smoking within the house while a mother was pregnant has a significant association with the occurrence

Table 3.3. Association between demographic characteristics and FC

Age group (year)	Cases N=150		Control N=150		OR	95%CI	P-value
	No.	%	No.	%			
3 month- <1	93	62.0	89	59.3	2.6	1.26-5.61	= 0.01
1-<3	37	24.7	25	16.7	1.8	0.73-2.88	NS
3-5	20	13.3	36	24.0	Reference group		
Gender							
Male	96	64.0	78	52.0	1.64	(1.03- 2.60)	=0.003
Female	54	36	72	48.0			
Residence							
Rural	32	21.3	19	12.7	1.87	1.0-3.48	0.046
Urban	118	78.7	131	87.3			

Table 3.4. Association between family history of FC and occurrence of FC

Family history among 1 st degree relatives	Cases N=150		Controls N=150		OR	95% C.I.	p-value
	No.	%	No.	%			
Positive	98	65.3	12	8.0	21.67	10.99-42.74	=0.001
Negative	52	34.7	138	92.0			
Family history among 2 nd degree relatives							
Positive	22	14.7	20	13.3	1.12	0.58-2.15	NS
Negative	128	85.3	130	86.7			

Table 3.5. Association between parental smoking and occurrence of FC

History of Mother smoking during pregnancy	Cases		Controls		OR	95% C.I.	p-value
	No.	%	No.	%			
Yes	12	8.0	10	6.7	1.22	0.51-2.91	NS
No	138	92.0	140	93.3			
Total	150	100%	150	100%			
History of father smoking							
Yes	35	23.3	5	3.3	8.83	3.35-23.25	=0.001
No	115	76.7	145	96.7			
Total	150	100%	150	100%			

Table 3.6. Association between maturity, birth weight and occurrence of FC

Maturity	Cases N=150		Controls N=150		OR	95% C.I.	p-value
	No.	%	No.	%			
Premature	15	10.0	19	12.7	0.77	0.37-1.57	NS
Full term	135	90.0	131	87.3			
Birth weight (gm)							
<2500	34	22.7	14	9.3	2.91	1.49-5.68	=0.001
≥2500	116	77.3	136	90.7			

of FC (P=0.001). Odd ratio indicates that paternal smoking play an important role in development of FC (OR=8.83, 95%CI=3.35-23.25).

Prematurity and low birth weight: Table (3.6) shows that there is no significant association between maturity at birth and development of FC. While the same table demonstrates that 22.7% of cases had low birth weight (<2500gm) compared to 9.3% among controls. Those children whose birth weight was less than 2500gm were more significantly liable to develop FC (P=0.0013, OR=2.91, 95%CI= 1.49- 5.68).

DISCUSSION

In the present study, FC cases were classified into two type's simple and complex FC. The majority of cases were simple FC (74.7%), and 25.3% were complex FC ; these finding are consistent with result of other study conducted in Lebanon at 2003, to determined classification and risk factors of recurrence of FC on 200 FC cases. This study showed that simple FC occurred in 76.3%, while only 23.7% of children had complex FC. Other studies showed the same findings. The present study found that gastroenteritis constituted about 39.3% of the causes of fever, 29.3% were due to urinary

tract infection, upper respiratory infection (14%), pneumonia (8%) and 7.3% had otitis media. Two cases had post vaccination fever (Measles, DPT). These finding are similar to a study conducted in Hong Kong at 2007. Such study found that gastroenteritis constituted (38.2%) , 27.3% were due to urinary tract infection, upper respiratory tract infection (13.1%), pneumonia (9.3%), 11.1% had otitis media and one case reported post MMR vaccination fever.¹ On the other hand, a cohort study was performed involving 379, children from USA at 2002, demonstrated that upper respiratory infection is a major cause of fever among FC cases (64.7%), pneumonia represented 17% and gastroenteritis about 9% . This difference may be due to a variation in the prevalence of diseases among countries. However, different studies have reported that vaccination is not a direct cause of FC. Moreover, another cohort study was conducted to determine the risk of seizures after receipt of DPT, MMR vaccination. It included reviews of the medical records of children with seizures who were admitted to four hospitals in England at 2001. This study reported that receipt of DTP vaccine was associated with an increased risk of febrile seizures only on the day of vaccination (relative risk=5.70; 95%CI= 1.98 - 16.42). While receipt of MMR vaccine had an increased risk of febrile seizures 8 to 14 days after vaccination (RR= 2.83; 95%CI= 1.44 to 5.55). Number of febrile seizures attributable to the administration of

DTP and MMR vaccination were estimated to be 6 - 9 and 25 - 34 per 100,000 children, respectively. As compared with other children with febrile seizures that were not associated with vaccination. The study also reported that children who had febrile seizures after vaccination was not found to be at higher risk for subsequent seizures and neurodevelopment disabilities or any adverse consequence.

The present study revealed that children age group between (3 months - <1 year) have significant association to develop FC (OR=2.62, 95%CI=1.26-5.61, P=0.01). A population-based cohort study conducted in Houston at 1997, which included 639 children who were followed from their first FC. The study found that younger age < 1year at first FC have more recurrence rate of FC than older age group (3-5years). In addition, Verity *et al.* mentioned that children age < 1year with FC have 50% chance of recurrence, comparing with a recurrence risk of only 20% if the first seizure occurred after the age of 3 years. Such authors attributed this fact to incomplete brain maturation during this age. Also the present study demonstrates that male gender is more liable for development of FC (OR=1.64, 95% CI=1.03- 2.06, P=0.003). A case-control study, which was conducted in Finland at 2003, demonstrated that male gender is more risky to develop FC (OR=1.9, 95%CI=1.0-3.7 P=0.0003). The investigator attributed that finding to the earlier maturation of female's brain. Moreover, a prospective cohort study was conducted in Japan at 1996 by Takayuki. Which included follows up of children from birth until six year of age (total number of children examined were 17,044). In this study the prevalence of FC in boys were higher than girls (11.2 %: 9.3 %) respectively. On the other hand, a case-control study conducted in England at 2007, by Sadleir and scheffur. Proved no association between gender and development of FC. The present study indicated that residence in rural area was significantly associated with occurrence of FC (OR=1.87, 95% CI= 1.0-3.84, P=0.046).

These finding agree with other population study which covered a children from Southern Taiwan at 1999, revealed that rural residence play important role in development of FC This association may be attributed to the low socioeconomic status of this area comparing to urban area, In addition, to high prevalence of illiteracy among families which means mismanagement of fever, and subsequently increases the risk for development of FC. Data observed from the present study shows that those children with family history of FC among first-degree relatives (parents, siblings), have 21 risk times to develop FC, with a significant association (OR=21.67, 95%CI=10.99-42.74. P=0.001). This finding is an accordance with another cohort study performed in Iran at 2001 by Telabian and Mohammadi They found a positive correlation between family history of FC among first-degree relatives and occurrence of FC (OR=2.43, 95%CI=1.32-4.56, P=0.036). This finding also mimic other results which has been conducted by Vanesch *et a l* and Dura -Travel *et al.* In addition, a study in USA, which has been conducted by Eric *et al*, in 1998; they found that those children with family history of FC have a significant genetic component for susceptibility to develop FC, these genes carried by chromosome 8q13-21. Thus, genetic factor plays an important role and considered as a fixed risk factor for occurrence of FC. On the other hand, the present study showed no significant association between family history of FC among second-degree relatives and development of FC, similar finding was reported in other

studies. One of the important environmental risk factor for the development of FC is prenatal exposure to cigarette smoking whether active or passive smoking (environmental smoking). The effect of prenatal smoking exposure on the risk of FC has been evaluated in 2 case- control studies; Berg *et al*, reported no association whereas, Cassano *et al*, found a 2 fold increase risk of FC in children whose mother exposed to smoking during pregnancy. However, this study fails to depict a significant association between exposure to cigarette smoke and development of FC, probably due to recall bias which is one of the important disadvantage of case-control study or because female smoking is not a common habit among Mosul society. The present study reported that father's smoking within household while mother is pregnant could play a significant risk in the development of FC. This finding is similar to a study that has been done in Denmark at 2005. Authors suggested that prenatal exposure to cigarette smoking whether active or passive may affect brain development and maturation during the fetal life and any sudden elevation in body temperature of child whose mother exposed to smoking during pregnancy may lead to attack of fit. Furthermore, Sidvenvall *et al.* suggested in their study that prenatal exposure to smoking may reduce fetal oxygenation and impaired fetal blood flow, which subsequently make the child more liable to develop FC, than others who were not exposed. The nature of relationship between birth weight and occurrence of FC is not completely clear, however, the present study clarified that children whose birth weight less than 2500 gm were more liable to develop FC. This comes in accordance with other study which has been conducted in Malaysia at 2001 by Ling, he suggested that the relationship between LBW and the development of FC, could be explained by the presence of intrauterine growth retardation among this group, which makes them more likely to experience hypoxia and consequently increases the risk of FC.

Conclusion

The following conclusions were obtained from the present study.

- Gastroenteritis constituted a major cause of fever among cases of FC.
- Three quarters (74.7%) of cases were simple febrile convulsion.
- The following factors were emerged as a risk predictors of development of FC among study sample: Family history of febrile convulsion among first-degree relatives (Exp B=27.21, P=0.001), fathers smoking (Exp B=8.84, P=0.001), family history of febrile convulsion among second-degree relatives(Exp B=2.52, P=0.01), rural residence (Exp B=2.20, P=0.01), degree of temperature >39° (Exp B=0.32, P=0.001), and children aged between 3-5 years (Exp B =0.69, P=0.05).

Recommendations

- 1- Reassurance of parents about the benign nature of this disorder
- 2- Educate parents about:
 - a) prognosis, causes and management of a case of FC.
 - b) Early management of fever play an important role to prevent of FC, hence, this issue should be a vital point in parent's education.

3- Further cohort studies are need to identify causal relation between the risk factors established in this study and development of FC, in addition, to other factors (iron deficiency anemia, history of developmental delay and number of episode of fever per year).

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