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Clinical Evaluation and Risk Factors of Recurrent Febrile Convulsion Among Iraqi Children: A Case-Control Study

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Original Article

ABSTRACT

Febrile convulsion is the most frequent type of seizures, this convulsion often associated with fever of extra-cranial origin. It affect 3 to 5% of children. Many risk factors contributed to incidence of febrile convulsion and its recurrence. This study aimed to identify the main risk factors associated with recurrence of febrile convulsion among group of Iraqi children younger than 6 years of age. Therefore, a case-control study was conducted during a period of one year included a total of 190 patient aged between 6months - 5 years with febrile convulsions who were referred to the emergency department of Central Pediatric Teaching Hospital in Iskan/Baghdad city of them 94 had recurrent febrile convulsion (two or more), (cases group) 96 had single febrile convulsion as control group. Data collected after all ethical issue approval from parents and ethical committee, full medical history was taken and thorough clinical examination was performed in addition to necessary investigations. Findings revealed that age younger than 12 months at onset of first febrile convulsion, being a male, having positive family history of FC in 1st degree relatives, positive family history of epilepsy, low temperature (≤ 39˚C) at the onset of the first febrile convulsion, and complex febrile convulsion were the main risk factors of recurrence of febrile convulsions among Iraqi children under 6 years age. Other factors showed no significant association with recurrence.

Keywords: *Febrile convulsion, Epidemiology, pathogenesis, types, risk factors, recurrence, management,*

1. INTRODUCTION

Febrile convulsions are the most frequent types of seizures, often associated with fever of extra-cranial origin; they are frequent in children between six months and five years of age and, according to the scientific literature, affect 3 to 5% of children and are more common in girls than in boys. Febrile convulsion occurs due to neurological functional events in neurologically-healthy child associated with febrile event of more than 38 degree centigrade without signs of intracranial infections and no other history of previous convulsion (1), Febrile convulsion considered as one of the common epileptic syndromes. Up to 4% of children developed at least one febrile convulsion attack during their childhood . Febrile convulsion is relatively more frequent in male than female children and in while than black population(2,3).

From a clinical point of view, febrile convulsion can be classified into two large groups: simple convulsion lasting less than 15 minutes and complex convulsion lasting more than 15 minutes. The convulsion can be tonic-clonic, tonic or clonic, almost always of a generalized nature and to a lesser percentage, of the focal (2,4,5). The treatment varies according to the presenting type of febrile convulsion. It is receive such importance that the treating doctor has extensive knowledge about this condition with regards to the clinical guidelines and its purposes(2,4) .

Definition

The National Institutes of Health (NIH) of the United States defines the febrile convulsion as a phenomenon of childhood/infancy that occurs during 6-60 months of age between six months and five years of age, related to febrile attack of (≥38 ° C), without an identifiable cause(6).

Simple febrile convulsion: also called typical or benign febrile seizure, is defined by the following characteristics: it occurs when there is a body temperature greater than or equal to 38°C; has one lasting no more than fifteen minutes ; it is generalized 8,9. It only occurs once in a 24- hour period , and it does not have an intracranial infection or serious metabolic disturbance as a possible explanation. the movements are tonic-clonic (uniform muscular contraction); it usually resolves spontaneously and may be accompanied by a history of FC in the family without history of Epilepsy (7,8)

Complex febrile convulsion: also called an atypical or complicated febrile convulsion, is one that has any of the following characteristics: duration greater than 15 minutes, two or more episodes in a 24- hour period including current state, which occurs in a child with a history of alterations in psychomotor development or with a family history of focal epilepsy (9–11).

Epidemiology

Febrile convulsion occurs more frequently in boys than in girls between 6 – 60 months of age, with highest incidence between 18 and the 24 months. No mortality due to febrile convulsion itself, nonetheless, some are reported due to some accompanied morbidity or complication. Family history for febrile convulsion has been reported in 25-40% of cases (7,12,13). The probability of presenting epilepsy in children with febrile convulsion is low, approximately between 2 and 5%, which is relatively more frequent than in general population . Convulsion are tonic-clonic in 55–94% of cases, tonic in 7–33%, and clonic in 3–28%. They are usually generalized in 90 to 93% of the episodes and, to a lesser extent, focal or hemi-corporal (1,3,14,15). Recurrence of the first febrile seizure in a child has been associated with a history of febrile and non-febrile seizures, developmental delay, viral infection, iron deficiency anemia, complex seizures. The patients with the highest risk are those who present a first attack before 12 months; These are conditions that can lead to predict the development of a febrile seizure in any patient, giving a 33% risk of recurrence after presenting the first seizure (5,6,12,14,16,17). Some vaccinations have been reported to be one of the predisposing factors in pediatric patients, since an increase of up to four times in the risk of febrile convulsion has been found in the period of one to two weeks after vaccination(18–20).

Pathophysiology:

The real pathogenesis of FC is unknown , however, several theories have been proposed, including the genetic, immunity and other mechanisms. Febrile seizure follows an autosomal dominant inheritance with an incomplete penetration pattern ; It can be presented as a multifactorial and polygenic inheritance distribution or not, and its phenotypic expression can be inhibited by other factors, and are environmental or genetic(21,22) One of the theories that has led several authors to investigate and inquire about the inheritance of this condition suggests the presence of a gene involved in the appearance of febrile convulsion . Another theory proposes that the nervous system has four types of histaminergic receptors - H1, H2, H3 and H4 - of which histamine 1 (H1) and histamine 3 (H3) receptors are involved in the decrease in seizure activity. Increase in histamine raises the threshold of attack and reduce the severity and the duration of the crisis, while at the block of H1 and H3 receptors with the administration of antihistamines, an effect occurs otherwise(23). Other research suggests that the cause may be related to the synthesis of gamma-aminobutyric acid (GABA), which decreases the temperature. The increase in temperature is the cause of many alterations at the cellular level that are usually caused by disruption of the Golgi

apparatus, edema of the mitochondria, change in cell permeability, or disruption of the nucleus and chromatin aggregation(24). In response to fever, all the living cells respond by the synthesis of heat shock proteins; synthesis of these proteins helps cells to protect themselves from the following lethal conditions. So that is triggered reduction of GABA, which compromised glycolysis mechanism(24,25)

Clinical manifestations

Simple febrile-convulsion may be associated with a rapid increase in core temperature of ≥ 39°C (6). Simple febrile-convulsion is a generalized lasts < 15 minutes and not recurrent within 24 hours and there is no evidence of neurological disorders after the attack. The complex FC mainly focal lasts for longer time and recurrent within 24 hours. Complex FC, usually related to subsequent neurological defects (such as Todd's paresis. These seizures account for approximately 15% of febrile-seizures episodes. At some points, a febrile seizure develops and prolonged for 30 minutes or more, or several brief seizures without improvement and regaining consciousness, this what called febrile-status-epileptics (3,6,8,26,27)

Management

Medical history should be taken thoroughly, then full clinical examination should be performed for both pediatric and neurological assessments. The cause of fever should be assessed and consciousness level should be identified, however, only necessary laboratory investigation should be performed when needed or when there is a suspicion and clinical evidence of possible diseases such as meningitis. Similarly, CT-scanning or MRI should not be performed on routine bases unless there is an evidence of underlying structural lesions (6,11,14,28).

Prognosis and outcome of febrile-convulsion:

Good prognosis usually reported with FC, however, almost 30% of cases with FC may have recurrence. nonetheless, the risk of recurrence decrease with advancing age of child (13,14). Risk of Epilepsy is rare, the risk is higher in cases with neurological abnormalities or delayed development prior to FC, children aged less than nine months at first attack are at higher risk to have epilepsy. Children with family history of epilepsy, complex convulsions are also at higher risk. The incidence of epilepsy in cases with no such risk factors is less than one percent while it much higher , reach almost 9%, when several risk factors are found simultaneously. Furthermore, previous studies reported that neurodevelopment disorders and autism should be considered infebrrile convulsion cases (29–32).

2. PATIENTS and METHODS

This was case-control study conducted in the central teaching hospital of pediatrics in Baghdad from 1st of October 2009 to the 1st of October 2010. A total of 190 patient aged between 6months - 5 years with FC who were referred to the emergency department of Central Pediatric teaching Hospital in Iskan were enrolled in this study , of them 94 had recurrent febrile convulsion(two or more) (cases group) and 96 had single febrile convulsion (control group). Data collected using a pre-constructed data collection sheet, variables included age at first FC, sex, family history of FC among 1st and 2nd degree relatives or Epilepsy, Fever grade at onset of FC, duration between the onset febrile attack and FC onset, convulsion type (simple or complex) and cause of fever were reported. Any patients with history of neonatal seizure or a febrile convulsion at any age were excluded from the study. For all patients in both groups , information about FC were taken including their age at 1st FC attack and categorized into three categories, 6 to 12 months, 13-24, and 25-36 and > 36 months, ,sex Family history of FC, family history of epilepsy .Duration between the onset of fever and onset of FC (<2 hr,2-24hr, >2 hr.),Height of temperature at onset FC (<39°C,>39 °C.),Types of the FC (simple or complex) and the real cause of fever. The information was obtained directly from mothers of patients. Our patients with recurrent FC (cases) were admitted to the hospital while those with single FC (control) some of them admitted to the hospital for other medical non relevant problem and other were selected from out patients department. Examination of CSF as well as serum calcium, blood sugar, blood urea, serum creatinine, general stool examination, stool culture, urinalysis and urine culture ,chest x-ray, electroencephalogram (EEG). And other investigations were performed accordingly. Development assessment has been done for all patients in both groups. Based on clinical examination and history, febrile convulsion was identified by exclusion of CNS infection in children with normal developmental characteristics after neurological examination and laboratory assessment according to the provisional diagnosis. For data management and analysis, statistical software package was adopted, SPSS 16, and Microsoft Excel program were used in all statistical circumstances. Appropriate statistical tests and analysis were performed accordingly. P. value (significance level) less than or equal to 0.05 (two-tailed) was considered.

3. RESULTS

Among cases, (63.8%) aged between 6-12 months compared to 54.2% in controls, distribution of cases and control across other age groups was almost close each other, however, a statistically significant difference had been found in distribution of age, (P<0.05). In both groups males were dominant with significant difference between both groups in sex distribution, (P<0.05), (**Table 1**). Family history of FC in 1st degree relative show significant (P < 0.05) , association with recurrence of FC 68.1% compared to 41.6% in control group. Patients with positive family history of FC in 2nd degree relative for both cases and control groups represented lower proportion, accounted for 41.5% in cases and 35.4% in controls and the difference was statistically insignificant, (P. value>0.05) as shown in (**Table 2**). Positive family history of epilepsy was reported in in 38.3% of cases and 19.8% of controls were with significant difference, (P<0.05), indicates that cases had more frequent family history of epilepsy (**Table 3**). Among cases , 55 patients (58.5%) had ≤39 ˚C temperature at onset of FC compared to 25 patients (26%), of control group. The remaining cases and controls had temperature less than more than 39 ˚C at onset of FC (**Table 4**). Regarding the time between onset of fever and onset of FC , more than half of attacks of FC in cases and controls occur between 2-24 hour of occurrence of fever, 56.3% and 63.2%, respectively, however, the difference did not reach the statistical significance, (P. value>0.05), (**Table 5**). Frequency of simple convulsion was significantly lower in cases group compared to controls; 47.9% and 66.7%, respectively, conversely, the complex type was more frequent in cases group, (P<0.05), (**Table 6**). Regarding the causes of fever, in both studied group the more frequently reported causes were upper respiratory infection and Pneumonia. Other causes of FC included gastroenteritis, UTI and post DTP vaccination were less frequent. However, no significant differences between both studied groups regarding the causes of FC, in all comparisons of causes, P>0.05, (**Table 7**)

Table 1. Age and sex distribution of both studied groups

Variable		Cases (N=94)		Controls (N=96)		P. value
		No.	%	No.	%	
Age (months)	6 - 12	60	63.8	52	54.2	0.011
	13 - 24	23	24.5	30	31.3	
	25 - 36	8	8.5	10	10.4	
	>36	3	3.2	4	4.2	
Total		94	100.0	96	100.0	
Sex	Male	66	70.2	54	56.3	0.046
	Female	28	29.8	42	43.8	
Total		94	100.0	96	100.0	

Table 2. Distribution of family history of FC in first and second degree relatives of cases and controls

Family history of FC		Cases (N=94)		Controls (N=96)		P. value
		No.	%	No.	%	
First degree relative	Positive	64	68.1	40	41.7	0.001
	Negative	30	31.9	56	58.3	
Total		100.0	100.0	96	100.0	
Second degree relative	Positive	39	41.5	34	35.4	0.476
	Negative	55	58.5	62	64.6	
Total		100.0	100.0	96	100.0	

Table 3. Distribution of Family history of Epilepsy among cases and controls

Family history of Epilepsy	Cases (N=94)		Controls (N=96)		P. value
	No.	%	No.	%	
Positive	36	38.3	19	19.8	0.008
Negative	58	61.7	77	80.2	
Total	94	100.0	96	100.0	

Table 4. Distribution of cases and controls according to the degree of temperature at onset of FC

Temperature (˚C)	Cases (N=94)		Controls (N=96)		P. value
	No.	%	No.	%	
≤39 ˚C	55	58.5	25	26.0	<0.001
> 39 ˚C	39	41.5	71	74.0	
Total	94	100.0	96	100.0	

Table 5. Distribution of cases and controls according to the time between onset of fever and FC

Time	Cases (N=94)		Controls (N=96)		P. value
	No.	%	No.	%	
< 2 hours	20	21.3	24	25.0	0.628
2 - 24 hours	53	56.4	61	63.5	
> 24 hours	21	22.3	12	12.5	
Total	94	100.0	96	100.0	

Table 6. Distribution of cases and controls according to the type of convulsion

Type of FC	Cases (N=94)		Controls (N=96)		P. value
	No.	%	No.	%	
Simple	45	47.9	64	66.7	0.013
Complex	49	52.1	32	33.3	
Total	94	100.0	96	100.0	

Table 7. Distribution of cases and controls according to the causes of convulsion

Cause of fever	Cases (N=94)		Controls (N=96)		P. value
	No.	%	No.	%	
Upper respiratory tract infection	55	58.5	52	54.2	0.647
Pneumonia	25	26.6	24	25.0	0.931
Gastroenteritis (Bloody andwatery diarrhea)	6	6.4	10	10.4	0.459
UTI	5	5.3	6	6.3	0.971
Post-vaccination (DTP)	3	3.2	4	4.2	0.978
Total	94	100.0	96	100.0	

4. DISCUSSION

Among the commonest causes of convulsions in children FC was the more frequent reported cause in children under six years of age. It represents an important anxious , concerns and apprehensive issue for parents regarding the recurrence of FC, this concerns and anxiety of parents attributed to inadequate knowledge about FC and fever. Febrile convulsion is benign process, yet diverse factors have been identified to increase risk of relapses. In this study we found that there are several risk factors that predicting the possibility of recurrent FC; age of less than 12 months at the onset of the first FC was associated with increased recurrence , these findings agreed that reported in previous studies conducted by Knudsen et al. (17) and Rantala and Uhari (33) . We found that males were more liable to have recurrent FC with case to control ratio of 1.4 to one and this was also documented by Bessisso et al. (16) and Ojha et al.(34), but this result is not compatible to what was found by Al-Eissa. (5) study who found that gender had no role in occurrence of recurrence of FC.

Family history of FC in 1st degree relatives of FC found to be a risk factor for recurrence of FC and this result consistent with earlier studies by Martin-Fernandez et al (35) , Offringa et al.(14) and Van et al. (12) . Family history of FC in 2nd degree relative did not serve as a risk factor for recurrence of FC and this finding consistent with finding of Van Esch et al. (12) Family history of epilepsy in our study seen to be a risk factor for recurrence of FC which agreed finding of Martin-Fernandez et al (35), Offringa et al. (14) studies.

Conversely, our findings disagreed that reported by Berg et al. (26) who founds that a family history of epilepsy did not increase the risk of recurrence of FC with case.

The present study found that low grade fever (≤39 ˚C) at the onset of first FC is a risk factor for recurrence of FC and this result supported the findings of Berg et al. (26) and Offringa et al.(14) In contrast, Al-Eissa (5) and Van et al. (12) where they found that low temperature was not a contributing factor for recurrence of FC. In our study, fever duration before the onset of first FC attack was not a risk factor for recurrence of FC and this finding did not agree with the result of Berg et al. (26) who founds that short duration (less than 2 hours) of fever before onset of first FC is a risk factor for recurrence. In our study, complex first FC is a risk factor for recurrence for recurrence which is comparable to that reported by Knudsen et al. (17) and and Al-Eissa (5) . But not consistent with Berg et al. (26) who found that complex febrile seizures did not increase the risk of recurrence FC. Regarding the cause of fever we found that cause of fever was not significant risk factor for the recurrence of FC , Consistently, Berg et al. (26) and Offringa et al.(15) concluded the same findings.

5. CONCLUSIONS

Different risk factors contributed to the recurrence of febrile convulsions , the main risk factors that increase the recurrence of FC were age younger than 12 months, at onset of first FC, being a male, having positive family history of FC in 1st degree relatives, positive family history of epilepsy, low temperature (≤ 39˚C) at the onset of the first FC, and complex febrile convulsion. Other factors including family history of FC in a 2nd degree relative , duration of fever (neither long nor short) before the onset of the first FC attack and cause of fever were not appeared to be significant risk factor for recurrence of FC.

Ethical Clearance

Authors declared that all ethical considerations were approved and undertake that all ethical issues and data collection were in accordance with the 2013 World Medical Association Declaration of Helsinki– Ethical Principles for Medical Research Involving Human Subjects

Conflict of interest: Authors declared none

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