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Original article

Update study on the risk factors of the first simple febrile seizure in children of Mosul, Iraq

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Abstract

Background: Simple febrile seizures are a common condition among children aged 6 months to 5 years. Many studies have been conducted on the risk factors for recurrence, while few studies have investigated the risk factors for the first simple febrile seizure. Our aim was to evaluate the risk factors of the first simple febrile seizure among children in Mosul City, Iraq.

Methods: This case-control study was conducted in a pediatric teaching hospital from January to May 2020 and included 120 patients who were admitted to the hospital with a first attack of simple febrile seizure; 120 age-matched children with febrile illnesses, but without seizures, were considered as controls. The cases and controls were compared to identify risk factors. A questionnaire interview with each parent/guardian, as well as necessary investigations, was performed. Odds ratios and t-tests were used for statistical analyses.

Results: Upper respiratory tract infection was the most common cause of fever in patients and controls. Nearly half of the patients were less than 2 years old. Significant associations were noted between young age, family history, bottle feeding, low hemoglobin levels, low birth weight, cesarean section, prenatal exposure to paternal smoking, and the first episode of simple febrile seizure.

Conclusion: Young age, artificial formula feeding, low hemoglobin levels, prenatal exposure to cigarette smoking, low birth weight, and cesarean section are likely risk factors for the first simple febrile seizure in Mosul City. To reduce the incidence of first simple febrile seizure, we recommend avoiding these possible risk factors.

Keywords

Artificial milk feeding, breastfeeding, children, first simple febrile seizure, risk factors, smoking.

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Introduction

Febrile seizures are the most common neurological disorder affecting infants and children aged from 6 months to 5 years. They are triggered by a rapid increase in body temperature [1]. The incidence is 3-4% in children and the affected child may develop at least one episode during childhood [2]. Febrile seizures are more frequent in boys than in girls [3]. Febrile seizures occur when the body temperature increases above 38°C (100.4°F). However, most cases have a fever of 39°C and above. Usually, the cause of fever is an underlying viral infection such as flu or roseola infantum [4, 5]. Fever may not be detected by the parents immediately prior to the seizure attack, but it should be detected post-ictally [6]. After the first attack, there is a 35% chance of recurrence [5]. Typically, febrile seizures affect an otherwise healthy child without any previous history of neurological symptoms, in the absence of any evidence of central nervous system infection, metabolic disturbance, or a previous afebrile seizure [6]. It may run in families [7]. Febrile seizures are classified into two types, simple and complex. Simple febrile seizures are characterized by generalized seizures, often tonic-clonic, but also clonic or simply as a sudden loss of contact with reality, and last usually less than 15 minutes. They do not recur during the first 24 hours [5, 8]. Most of these seizures last less than 5 minutes and the child recovers rapidly within an hour to the baseline status [7]. Febrile seizures are classified as a complex type when the attack has focal symptoms, lasts longer than 15 minutes, or has a recurrence within the first 24 hours [5, 7]. Most febrile seizures occur among children aged 12-18 months. It is proposed that at this young age, the developing brain has a low threshold for seizures and is more sensitive to rapid rises in body temperature. When this is combined with genetic predisposition and some environmental factors, the risk for a febrile seizure will increase. The older the affected child is at the onset of the first attack, the less likely it is to have a recurrence as less time remains to reach the upper age limit (5 years). Signs of typical simple febrile seizures include loss of consciousness, rolling up or deviation of eyes to one side, generalized body and limb stiffness, and shaking [5]. The diagnosis depends upon the exclusion of central nervous system infection or metabolic disturbances, as well as verifying the absence of any previous afebrile seizure. This may be performed by a detailed history and an appropriate physical examination to identify the cause of the fever [5, 6]. If a child has recovered from a seizure attack and acts normally, then meningitis or encephalitis is unlikely, and lumbar puncture for cerebrospinal fluid examination is often unnecessary [5]. Blood investigations, brain imaging, or electroencephalography are usually not recommended [9]. Lumbar puncture is indicated if there are obvious clinical features of meningitis. However, it is an option for children younger than 12 months when they appear otherwise normal and without signs and symptoms of meningitis, since these features may be atypical, if the child does not return rapidly to their normal status, or if they were not vaccinated against *Haemophilus influenzae* and pneumococcal bacteria [9]. Despite the benign and self-limiting character of simple febrile seizures, they are often associated with fear and concerns from the parents [6, 10]. The prognosis of simple febrile seizures is excellent, and the affected child will outgrow the problem by the age of 5 years. Simple febrile seizures do not cause cognitive disability or learning problems and do not increase the risk of mortality. However, there is a slight increase in the risk of epilepsy (2%) compared to the other children in the community [11]. Most simple febrile seizures last a few minutes and end before the patient reaches the hospital. For this reason, anticonvulsants such as benzodiazepines are usually not required. In cases with longer seizure duration, these medications might be needed to stop the seizure attack. Antipyretic medicine is ineffective in preventing the recurrence of febrile seizures. However, prehospital or home rescue management of these children could be performed by their parents using a diazepam suppository to stop the seizure episode. Owing to their serious adverse effects that outweigh the benefits, anticonvulsants are not recommended to prevent the recurrence of these seizures [12]. The exact pathophysiology of febrile seizures is unclear [6]. However, many studies have investigated the risk factors associated with the development of febrile seizures, either those preceding the first episode or provoking their

recurrence. Febrile seizures represent a significant problem among the children of Mosul. Therefore, in the present study, we aimed to identify the risk factors associated with the development of the first simple febrile seizure among children in Mosul, Iraq. These include gender, family history, low birth weight, low hemoglobin levels, prenatal exposure to paternal smoking, and feeding patterns.

Patients and methods

This hospital-based, case-control study was conducted in Mosul City from January to May 2020. The local Medical Research Ethics Committee approved the study and the study is consistent with the declaration of Helsinki. One hundred and twenty children aged 7-59 months who were admitted to the hospital with a history of first episode of seizure associated with fever and who fulfilled the criteria of simple febrile seizures were enrolled in the study [13]. The inclusion criteria include fever associated with a generalized seizure event lasting less than 15 minutes, a rapid recovery within 1 hour, no recurrence in the first 24 hours, and no evidence of central nervous system infection. Another 120 age-matched children with various febrile illnesses, but without a history of seizures, who were admitted to the pediatric wards nearly at the same time, were selected as controls. Informed written consent was obtained from the parents. A full history and physical examination were performed on the patients with febrile seizures to determine the causes of the fever as well as to exclude meningitis or any underlying neurological problems. Cases with confirmed meningitis, children who experienced afebrile seizures, or those with complex seizures were excluded from the study. The axillary temperature of cases and controls was measured by an electronic digital thermometer, and considered as "corrected body temperature" by adding 0.5°C. To confirm the cause of the fever, investigations such as complete blood count, blood culture, serum sodium, serum calcium, urinalysis and culture, random blood sugar, and, in certain instances, cerebrospinal fluid examination, were performed. Of the 120 cases, 21 required lumbar puncture because of suspicious clinical features indicating meningitis. However, cerebrospinal fluid examination of all these cases was normal. Assessment of the risk factors for the first attack of simple febrile seizures included a questionnaire conducted via an interview with each parent of both cases and controls, including the family history of simple febrile seizure, mode of delivery, maturity and birth weight, feeding pattern of the breast or formula milk, breastfeeding duration during the first 2 years of life, and exposure to tobacco smoking during pregnancy. To identify the risk factors associated with the development of the first simple febrile episode, both cases and controls were compared. To estimate the statistical significance of the risk factors, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The significance of the differences in the mean values was estimated using t-tests. The results were considered significantly different if the p-value was < 0.05. All statistical analyses were performed using IBM® SPSS® Statistics for Windows® version 23 (IBM Corp., Armonk, NY, USA) [14].

Results

Of the 120 patients with simple febrile seizure, 64 (53.3%) were younger than 24 months, while 56 (46.7%) were older. Corresponding to this age limit, 45 (37.5%) of the control group were under the age of 24 months, and 75 (62.5%) of them were older (**Tab. 1**).

The majority of children in the case and control groups were boys (61.7% and 55%, respectively). Regarding the residence of the enrolled children, both cases and controls were more frequently from urban areas (65.8% and 60%, respectively) than from rural areas.

Most of the diseases that caused fever were viral. Upper respiratory tract infection was the cause of fever in 64.2% of cases and 60% of controls.

Regarding the height of fever, 71 children (59.2%) of the case group had body temperatures ranging from 38°C to 39°C, while the remaining 49 (40.8%) had a temperature of more than 39°C. Compared with the control group, no statistically significant difference was found ($p = 0.514$).

In the majority of cases ($n = 73$, 60.8%), fever was recognized by their parents within less than 12 hours before the seizure event. In the remaining 47 children (39.2%), fever was noticed earlier than 12 hours before the seizure attack (**Tab. 2**).

Of the 120 cases of seizure attacks that occurred at home, 12 were rescued by their families by placing diazepam suppositories prior to reaching the hospital. These parents had high education and some of them were working in health care.

Compared with the control children, the children with the first febrile seizure were significantly younger: 20.75 ± 15.50 months vs. 27.37 ± 14.86 months (mean ± SD, $p < 0.001$) (**Tab. 3**).

Table 1. Demographic and clinical characteristics of cases versus controls.

Characteristics		Cases (n = 120)	Controls (n = 120)
Age range (months)		7-59	6-60
Age	**< 24 months**	64 (53.3%)	45 (37.5%)
	> 24 months	56 (46.7%)	75 (62.5%)
Gender	**Male**	74 (61.7%)	66 (55%)
	Female	46 (38.3%)	54 (45%)
Region	**Rural**	41 (34.2%)	48 (40%)
	Urban	79 (65.8%)	72 (60%)
Causes of fever		Upper respiratory tract infection – 77 (64.2%) Roseola infantum – 13 (10.8%) Gastroenteritis – 11 (9.2%) Urinary tract infection – 8 (6.7%) Otitis media – 6 (5%) Pneumonia – 5 (4.2%)	Upper respiratory tract infection – 72 (60%) Pneumonia – 15 (12.5%) Otitis media – 12 (10%) Gastroenteritis – 9 (7.5%) Urinary tract infection – 6 (5%) Roseola infantum – 6 (5%)

Data are presented as n (%) if not otherwise specified.

Table 2. Fever degree and its onset before the seizure attack.

Fever characteristics		Cases (n = 120)	Controls (n = 120)
Fever degree	**38-39°C**	71 (59.2%)	66 (55%) [a]
	> 39°C	49 (40.8%)	54 (45%)
Onset of the fever before the seizure attack	**< 12 hours earlier**	73 (60.8%)	-
	12-24 hours earlier	26 (21.7%)	-
	24-48 hours earlier	21 (17.5%)	-

Data are presented as n (%).
[a] Differences in fever degree are statistically not significant (p = 0.514).

Table 3. Cases versus controls in risk factors for the first simple febrile seizure.

Risk factor		Cases (n = 120)	Controls (n = 120)	95%CI	p-value
Age (months), mean ± SD		20.75 ± 15.50	27.37 ± 14.86	2.758 to 10.481	**0.0009**
Gender	**Male**	74 (61.7%)	66 (55%)	-7.11 to 16.81	0.425
	Female	46 (38.3%)	54 (45%)		
Family history		46 (38.3%)	8 (6.7%)	3.886 to 19.488	**< 0.001**
Region	**Rural**	41 (34.2%)	48 (40%)	-6.315 to 17.75	0.350
	Urban	79 (65.8%)	72 (60%)		
Hemoglobin (g/dL), mean ± SD		10.80 ± 1.35	11.40 ± 1.25	0.269 to 0.930	**0.0004**
Temperature	**38-39°C**	71 (59.2%)	66 (55%)	0.710 to 1.977	0.514
	> 39°C	49 (40.8%)	54 (45%)		
Caesarean section		56 (46.7%)	32 (26.7%)	1.4013 to 4.1319	**0.001**
Prematurity		21 (17.5%)	9 (7.5%)	1.144 to 5.979	**0.022**
SGA		17 (14.2%)	6 (5%)	1.352 to 10.654	**0.0113**
Breastfeeding in the first 24 months		19/64 (29.7%)	24/45 (53.3%)	1.2235 to 5.9884	**0.014**
Breastfeeding duration (months), mean ± SD		14.4 ± 8.5	17.3 ± 4.6	-4.638 to -1.1612	**0.001**
Paternal smoking during pregnancy		62 (51.7%)	35 (29.2%)	1.5248 to 4.4199	**0.0004**

Data are presented as n (%) if not otherwise specified.
Odds ratio was used for estimation of significance in risk factors between numbers, T-test was used for differences in the means.
CI: confidence interval; SGA: small for gestational age.

Of the 120 cases, 56 (46.7%) were delivered via cesarean section versus 32 (26.7%) in the control group ($p = 0.001$).

Thirty-eight patients had a history of low birth weight (less than 2,500 g). Of these cases, 21 (17.5%) were born prematurely at < 37 weeks gestation, while 17 (14.2%) were born small for gestational age (SGA). Of the control children, 9 (7.5%) were born prematurely and 6 (5%) were born SGA ($p < 0.05$) .

At 2 years of age, 19 of 64 cases (29.7%) and 24 of 45 controls (53.3%) were breastfed, and a complement diet was added when they were older than 6 months. The remaining 45 cases and 21 controls were fed formula milk. Statistically, a significant difference was noted between the two groups regarding breastfeeding ($p = 0.014$).

About one-third of the cases (46, 38.3%) had a positive family history of febrile seizures in 1st and 2nd degree relatives, while only 8 (6.7%) of the control group reported a family history of febrile seizure. The difference in the frequency of family history between the two groups was statistically significant ($p < 0.001$). In addition, the mean duration of breastfeeding for those breastfed children was significantly shorter ($p = 0.001$) in cases than in controls (14.4 ± 8.5 months vs. 17.3 ± 4.6 months, mean ± SD).

In 35 (29.2%) cases and 22 (18.3%) children in the control group, complete blood counts showed hypochromic microcytic anemia (low hemoglobin% < 11 g/dL, low MCV, low MCHC) [15].

In addition, the mean hemoglobin levels for all children in the case group were significantly lower than the mean hemoglobin levels of the control group (10.80 ± 1.35 g/dL vs. 11.40 ± 1.25 g/dL, $p < 0.001$).

All mothers in both cases and controls claimed to not have been smoking during pregnancy. Mothers of 62 of the cases (51.7%) had long exposure to passive smoking from their husbands while they were pregnant. Only 35 mothers (29.2%) of the control group reported exposure to passive smoking. The difference between the two groups in the frequency of paternal smoking was significant ($p < 0.001$).

Discussion

Although simple febrile seizure is a benign condition, it may cause fear and anxiety in parents. Therefore, it is important to study the risk factors associated with the first episode of simple febrile seizures. In this study, young age, family history of febrile seizure, bottle feeding during the first 24 months of life, low birth weight, cesarean section, low hemoglobin level, and paternal smoking during pregnancy are identified as possible risk factors for the first simple febrile seizure.

Our study revealed that children with first simple febrile seizures were significantly younger than controls, and about half of the cases were younger than 2 years. A similar result was reported by Leung and Robson [5], and the American Academy of Pediatrics [16] reported that the incidence of simple febrile seizure is higher in children younger than 2 years. We suggest that the developing brain of these children is more sensitive to fever and has a low threshold level for seizure attacks.

In our study, although the frequency of male cases was higher than of female cases, gender had no significant effect when compared with the controls. However, a higher incidence in males was reported in a study conducted by Pathan et al., who revealed a male-to-female ratio among cases of 2:1 [17].

Our study shows that a family history of 1st and 2nd degree relatives was a significant risk factor for the first simple febrile episode. Similarly, Sharawat et al. found that a family history of febrile seizure in 1st and 2nd degree relatives could be a significant risk factor for the development of the first simple febrile seizure [10]. We suggest that family history might indicate the presence of a link between genetic factors and a lower threshold for febrile seizures.

We also show that cases with a history of premature delivery or low birth weight were more prone to a simple febrile seizure. Consistent with our findings, Ellatif and Garawamy concluded that prematurity is a major risk factor [18]. Prematurity or low birth weight may contribute to incomplete brain myelination and may consequently reduce the threshold for febrile seizures [19].

Young age, prematurity or low birth weight, and cesarean section may share the same underlying predisposing cause that reduces the seizure threshold. This could be due to the immaturity of the brain or myelination, which are associated with these risk factors.

Another significant risk that our study explored is paternal smoking and its contribution to febrile seizures. Cigarette smoking is not a common habit among women in our society, so we felt it was difficult to explore the accurate prevalence of smoking in mothers. However, smoking is common among men. Our study showed that long-term

exposure of pregnant mothers to cigarette smoke has a significant association with the first febrile seizure, especially in cases of low birth weight. This finding is consistent with a study from Vestergaard et al., who showed that prenatal exposure to cigarette smoking may have a harmful effect on the fetal brain and may subsequently contribute to the first febrile seizure [20].

In this study, a significant association was found between low mean hemoglobin levels and the first simple febrile seizure. All our cases or control children with low hemoglobin levels were tested for hypochromic microcytic anemia, and we suggest that anemia was mostly a result of iron deficiency. The same findings were obtained by Vaswani et al. and Papageorgiou et al., who determined iron deficiency as a risk for the first febrile seizure [21, 22]. In contrast to our findings, Youseffichaijan et al. concluded that iron deficiency can prevent febrile seizures [23].

Our study considered cesarean section as a possible risk factor for the first simple febrile seizure. This result is consistent with the study of Hydarian et al. [24], while Yousif et al. did not consider cesarean section as a risk factor [25].

In this study, the role of the feeding pattern during the first 2 years of life was also evaluated. We found that the majority of cases under the age of 2 were fed with artificial formula milk since birth and continued to receive artificial formula milk after 6 months when semisolid food was added. On the other hand, breastfed children were significantly less frequent among cases when compared with controls during the first 24 months of life. We suggest that breastfeeding can help reduce the risk of the first febrile seizure. Similar to our findings, Mitsula et al. studied the role of breastfeeding during the first 12 months of life for the first febrile seizure. The authors concluded that breast milk might play a role in preventing first simple febrile seizures [26]. It has been reported that breast milk feeding plays an important role in brain development and the stabilization of neuronal membranes and consequently contributes to elevating the threshold for seizures. Furthermore, breast milk has an immunoprotective effect against viral illnesses that can cause fever in children.

The limitations of the study include the following: First, it is difficult to uncover the real frequency of cigarette smoking habit of the mothers. Second, a few patients refused lumbar puncture as a procedure to exclude meningitis, which delayed the diagnosis of febrile seizure. Finally, third, some parents found it challenging to define the onset of the fever before the seizure attacks.

Conclusion

Our study suggests that many possible risk factors might be associated with the development of the first simple febrile seizure in children in Mosul City. These include young age, low birth weight, family history of febrile seizure, cesarean section, bottle feeding, low hemoglobin levels, and prenatal exposure to paternal smoking. To reduce the incidence of first simple febrile seizures, we recommend avoiding possible risk factors such as exposure to paternal cigarette smoking, and to reduce the rate of cesarean section as much as possible, as well as encouraging breastfeeding and complete vaccinations. In addition, reassurance of the parents about the benign nature and good prognosis of simple febrile seizures is required.

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Declaration of interest

The Author declares that there is no conflict of interest. Funding: none.

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