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ORIGINAL ARTICLE

A Biochemical and Health Perspective on the Recurrence of Febrile Seizures in Children: Identifying Risk Factors and Clinical Outcomes

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KEYWORDS

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ABSTRACT: Febrile seizure (FS) is a common health issue among pediatric populations. Although it is generally benign and self-limited, recurrence is frequent and can cause significant stress for the child's family. Identifying the risk factors for recurrent FS can help facilitate preventive measures. This study aimed to investigate the incidence of recurrent FS and its associated risk factors in a sample of Iraqi children. This prospective, longitudinal study was conducted in the Department of Pediatrics at AL-Nassiriyah Child and Maternity Hospital, Thi-Qar Governorate. A total of 264 children (105 males and 159 females), aged between 6 months and 5 years, who presented with their first episode of FS, were included in the study. Demographic and clinical data were collected through direct interviews with the parents. The children were followed up every three months for one year to monitor for recurrent FS. Out of the 264 children, 84 (31.82%) experienced recurrent FS. Multivariate logistic regression analysis revealed that older age at the time of the first seizure (odds ratio [OR] = 0.42, 95% confidence interval [CI] = 0.24–0.71, p = 0.012), longer duration of fever (OR = 0.34, 95% CI = 0.18–0.63, p = 0.009), and higher body temperature (OR = 0.16, 95% CI = 0.05–0.51, p = 0.002) were protective factors against recurrent FS. On the other hand, family history of FS (OR = 2.12, 95% CI = 1.16–3.86, p = 0.014), complex seizures (OR = 10.46, 95% CI = 4.82–22.71, p < 0.001), and iron deficiency (OR = 2.7, 95% CI = 1.6–4.87, p = 0.001) were identified as independent risk factors for recurrent FS. Recurrent FS occurs in approximately one-third of children with FS following a three-month follow-up period. Risk factors for recurrent FS include a younger age at the first episode, lower temperature during the seizure, a brief period between the initial seizure and the onset of fever, iron deficiency, and a family history of FS. These findings could help inform strategies for preventing recurrent FS in pediatric patients.

INTRODUCTION

Febrile seizures (FS) are a common disorder in children, typically occurring when body temperature rises above 38°C (100.4°F) [1]. These seizures generally manifest between the ages of 6 months and 5 years, and are classified into two types: simple and complex. Simple seizures are generalized tonic-clonic convulsions, without focal features, lasting less than 15 minutes, and without recurrence within the following 24 hours, while complex

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seizures may last longer than 15 minutes and present with focal features [1, 2]. Although FS is typically a benign and self-limited condition, about one-third of affected children experience recurrent seizures, which can lead to increased concerns for both families and healthcare providers [3]. Recurrent FS can be associated with further neurological issues and even an elevated risk of developing long-term disorders. Therefore, identifying risk factors for recurrent febrile seizures is crucial, as this knowledge can guide physicians in implementing more effective preventive and therapeutic measures [3]. The pathophysiology of FS is not yet fully understood, but several theories have been proposed regarding the mechanisms underlying febrile seizures [4]. Febrile seizures, which occur in children over one month old during a febrile episode, affect 2% to 4% of children in the United Kingdom and the United States, with a recurrence rate of 30% [4]. Genetic and epigenetic factors play a crucial role in the onset of febrile seizures (FS). Mutations in certain genes, such as SCN1A and GABRG2, can lower the threshold for neuronal excitability, increasing the risk of seizures [4]. Meanwhile, epigenetic changes, including DNA methylation and gene expression regulation, can be influenced by environmental factors like fever and stress, contributing to the development of this disorder [5]. One such theory is based on the stimulation of the central nervous system in response to fever and a rapid increase in body temperature. Fever can alter the seizure threshold in the brain, triggering the onset of seizures [4]. In this process, temperature changes activate ion channels in neurons, leading to heightened electrical activity in the brain [4]. Additionally, fever can induce the release of chemical mediators such as glutamate and other neurotransmitters, which stimulate the nervous system and contribute to seizure development [5]. Other theories focus on the role of the immune system and inflammation. Some studies suggest that alterations in immune system activity and an increase in cytokine release during febrile seizures can result in brain tissue damage and the onset of seizures. Furthermore, metabolic disorders such as iron deficiency have been identified as potential underlying factors for FS, as they may indirectly influence neural excitability [6].

In Iraq, although FS is a common issue among children, research on its prevalence and the risk factors for recurrence in this population remains limited and fragmented. Thus, the present study aims to investigate the prevalence of recurrent febrile seizures and identify associated risk factors in Iraqi children. This study could enhance awareness of the disorder in the region and provide valuable insights for therapeutic and preventive strategies for FS.

MATERIALS AND METHODS

Patients and methods

Setting and design

This is a prospective, longitudinal study which was conducted in department of Pediatrics, AL- Nassiriya Child and Maternity hospital, Thi-Gar governorate. The study included all children 6 months to 5 years of age; attending the department from February 2016 to January 2017 presenting with their first FS. Those children were followed up every 3 months for 1 year to look for recurrence.

Inclusion criteria

This includes children between 6 months- 5 years presenting with seizure and fever without central nervous system infection.

Exclusion criteria

Previous FS, intracranial infectios. Intracranial infection was confirmed through: cerebrospinal fluid culture to isolate the microorganisms, biochemical changes in CSF such as increased number of white cells; high protein or low glucose, Gram stain of CSF to look for microorganisms, blood culture to isolate the microorganisms.

Initially, the study included 320 children presenting with seizure. Of those 56 children were excluded (36 cases of meningoencephalitis and 20 cases of cryptogenic unprovoked seizures). Thus, the eligible patients were 264 children which fulfilled the inclusion criteria.

Evaluation and data collection

According to hospital policy, all children with FS are admitted till they are stable. Parents were interviewed using predesigned questionnaire. Full physical and neurological examinations were done. Electroencephalography (EEG); CSF examination was done when required; also computed tomography (CT); and magnetic resonance imaging (MRI) were done when required to determine the cause of the seizure. Seizures were classified as complex and simple.

Data analysis

SPSS software (v. 26) was used. Each variable was categorized in to two or more variables. The univariate analysis was performed using Pearson Chi square. A p-value of ≤ 0.05 was considered significant.

RESULTS

Incidence of recurrent febrile seizure

Out of 264 children, FS was recurrent in 84 children (31.82%) as shown in Figure 1.

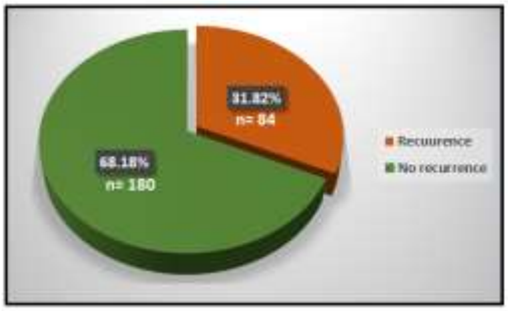

Figure 1. incidence of FS among children.

Association of demographic characteristics with FS recurrence

Four demographic characteristics (out of six) were significantly associated with FS recurrence. First seizure age ≥ 24 m and fever duration ≥ 1 hr were less common among patients with recurrent FS (35.71% and 67.85%, respectively), than those without recurrent FS (57.22% and 84.44%, respectively) with highly significant differences. Furthermore, higher body temperature (>104 F) was less frequent in children with recurrent than those without recurrent FS (8.33% vs. 20.56%) with a significant difference. In contrast, family history of FS was more common in children with recurrent FS (38.1%) than those without recurrent FS (20%) with a highly significant difference (Table 1).

Table 1. Association of demographic characteristics with FS recurrence.

Risk Factors	With non-recurrence (n= l80)	With recurrence (n= 84)	Total (n=264)	p-value
Sex				
Male	75(41.67%)	30(35.71%)	105(39.77%)	0.357
Female	105(58.33%)	54(64.29%)	159(60.23%)	
Age at first seizures, m				
<24	77(42.78%)	54(59.52%)	131(49.62%)	**0.001**
≥24	103(57.22%)	30(35.71%)	133(50.38%)	
Duration of fever, hr				

<1	28(15.56%)	27(32.14%)	55(20.83%)	**0.001**
≥1	152(84.44%)	57(67.85%)	209(79.17%)	
Temperatures, F				
101	9(5%)	11(13.1%)	20(7.58%)	
102	39(21.67%)	19(22.62%)	58(21.97%)	
103	44(24.44%)	24(28.57%)	68(25.76%)	
104	51(28.33%)	23(27.38%)	74(28.03%)	**0.033**
>104	37(20.56%)	7(8.33%)	44(16.67%)	
Family history of FS				
Absent	144(80%)	52(61.9%)	196(74.24%)	**0.002**
Present	36(20%)	32(38.1%)	68(25.76%)	
Duration of seizure, min				
>15	15(8.33%)	12(14.29%)	27(10.23%)	0.137
<15	165(91.67%)	72(85.71%)	237(89.77%)	

Association of clinical characteristics with FS recurrence

Thirty-two children with recurrent FS (38.1%) had complex type of seizure compared with only 5.56% of non-recurrent FS who had such type, with a highly significant difference. Moreover, the iron deficiency and family history of epilepsy were more frequently registered in children with recurrent FS (71.4% and 7.14%, respectively) than those without recurrent FS (47.22% and 1.11%, respectively) with highly significant differences (Table 2).

Table 2. Association of clinical characteristics with FS recurrence

Risk Factors	With non-recurrence (n= l80)	With recurrence (n= 84)	Total (n=264)	p-value
Type of seizures				
Simple	170(94.44%)	52(61.9%)	222(84.09%)	**<0.001**
Complex	10(5.56%)	32(38.1%)	42(15.91%)	
Neurodevelopmental disorders				
Absent	170(94.44%)	83(98.81%)	253(95.83%)	0.098
Present	10(5.56%)	1(1.91%)	11(4.17%)	
History of recent vaccination				
Absent	163(90.56%)	73(86.9%)	236(89.39%)	0.370
Present	17(9.44%)	11(13.1%)	28(10.61%)	
Iron deficiency				
Absent	95(52.78%)	24(28.57%)	119(45.08%)	**<0.001**
Present	85(47.22%)	60(71.43%)	145(54.92%)	
Family history of epilepsy				
Absent	178(98.89%)	78(92.86%)	256(96.97%)	**0.008**
Present	2(1.11%)	6(7.14%)	8(3.03%)	

Multiple Logistic regression

In order to find out the independent factors associated with recurrent FS, multiple logistic regression was used. All demographic and clinical factors that had a significant association with recurrent FS in the univariate analysis were entered the model. According to the results, each of older age at first seizure (OR= 0.42, 95%CI= 0.24-0.71, p= 0.012), longer duration of fever (OR= 0.34, 95%CI= 0.18-0.63, p= 0.009) and higher body temperature (OR= 0.16, 95%CI= 0.05-0.51, p = 0.002) are protective against recurrent FS. On the other hand, each of family history of FS (OR= 2.12, 95%CI= 1.16-3.86, p= 0.014), complex seizure (OR= 10.46, 95%CI= 4.82-22.71, p<0.001) and iron deficiency (OR= 2.7, 95%CI= 1.6-4.87, p= 0.001) are independent risk factors for recurrent FS (Table 3).

Table 3. Multiple logistic regression

Risk Factors	Beta-coefficient	OR	(95%CI)	p-value
Age at first seizures, m				
<24m		1.0		
≥24m	-0.879	0.42	0.24-0.71	0.012
Duration of fever, hr				
<1		1.0		
≥1	-1.08	0.34	0.18-0.63	0.009
Temperatures, F				
101		1.0		0.045
102	-0.92	0.4	0.14-1.12	0.082
103	-0.81	0.45	0.16-1.23	0.118
104	-0.99	0.37	0.13-1.0	0.053
>104	-1.87	0.16	0.05-0.51	0.002
Family history of FS				
Present		1.0		
Absent	0.750	2.12	1.16-3.86	0.014
Type of seizures				
Simple		1.0		
Complex	2.34	10.46	4.82-22.71	<0.001
Iron deficiency				
Present		1.0		
Absent	1.1	2.79	1.6-4.87	0.001
Family history of epilepsy				
Present		1.0		
Absent	1.37	3.92	0.73-21.04	0.111

DISCUSSION

The present study only briefly mentions the alignment of its results with previous studies, without providing a detailed comparison of the identified risk factors with other research. In this study, the recurrence rate of febrile seizures (FS) was found to be 31.82%. Globally, the recurrence rate of FS ranges from 27% to 55.3% [7-9]. However, this rate varies significantly across different regions. For instance, in a study conducted in Korea by Byeon et al. [10], the prevalence peaked in the second to third year of life, at 27.51%. In an Iranian study by Kazemi et al. [11], the recurrence rate of FS was 25.7% during a one-year follow-up. In Denmark, the cumulative risk of recurrent FS was 22.7% following the first episode [12]. Additionally, a study conducted by Kumar et al. [13] in India found that out of 528 children, 174 (32.9%) experienced recurrent FS. The recurrence risks observed in our study align somewhat with the previously reported ranges, although estimates differ across the studied populations. These variations are primarily related to the follow-up duration after the first episode. Generally, the longer the follow-up period, the higher the recurrence rate. Furthermore, variations in demographic characteristics and risk factors contribute to the broad range of recurrence rates observed. In the present study, factors such as age at first seizure under 1 year, fever duration under 1-hour, lower temperature during seizure, iron deficiency, and complex seizure were identified as independent risk factors for recurrent FS. In a previous local study by Alwan and Hussein [14], younger age at onset, male sex, low temperature, and frequent febrile convulsions were found to be risk factors for recurrent FS. According to an Iranian study by Kazemi et al. [11], similar findings were reported.

Moreover, a study conducted in Thailand by Kantamalee et al. [15] found that younger age at onset of FS increased the risk of recurrence. A recent study in Turkey involving 300 children with FS identified several risk factors for recurrence as well as the development of epilepsy. These included temperature before the seizure (<39ºC), the interval between fever and seizure (<1 hour), younger age at the first FS, type of FS (complex), duration of the seizure (>15 minutes), neurodevelopmental delay, and abnormal EEG recordings [16&17].In another study, it was observed that children with FS had a higher frequency of iron deficiency compared to children with fever but no seizures [18].Despite the relative variation in studies regarding the risk factors for recurrent FS, there is almost universal agreement about the role of low-grade fever, shorter fever duration, and younger age at the first episode as risk factors for recurrence. This suggests that such patients have a lower seizure threshold, where even a moderate rise in temperature for a short duration can trigger convulsions [19,20]. These discrepancies between different studies can be attributed to several factors, with the most significant being the duration of the follow-up period, differences in ethnicity, and variations in the anthropometric factors of the patients [21-24]. These findings highlight the importance of understanding neurological disorders and diseases, as identifying risk and protective factors can aid in early diagnosis, better management, and reducing neurological complications in children.

CONCLUSIONS

The present study revealed that approximately one-third of children with febrile seizures (FS) experience recurrent FS following a three-month follow-up period. Identified risk factors for recurrent FS include a younger age at the time of the first episode, lower temperature during the seizure, a short period between the initial seizure and the onset of fever, iron deficiency, and a family history of FS. On the other hand, factors such as older age at the time of the first seizure, longer fever duration, and higher body temperature during the seizure were identified as protective factors against recurrent FS. These findings could help inform strategies for preventing recurrent FS in pediatric patients.

CONFLICT OF INTERESTS

No conflict

REFERENCES

1. Weng J., Chen W., Zhu M., 2024. Seizure-like symptoms induced by hypomagnesemia in a patient with incomplete small bowel obstruction; A case report: Hypomagnesemia causes seizure due to bowel obstruction. Galen Med J. 13, e3350. doi: 10.31661/gmj.v13i.3350.
2. Kılıç B., 2019. Clinical features and evaluation in terms of prophylaxis of patients with febrile seizures. Sisli Etfal Hastan Tip Bul. 53(3), 276-283.
3. Mikati M.A., 2012. Febrile seizures. In: Behrman RE., Kliegman RM., Jenson HB., eds. Nelson Textbook of Pediatrics. 19th ed. Philadelphia, PA: Nwb Saunders Co; 586, 2017.
4. Whelan H., Harmelink M., Chou E., 2017. Complex febrile seizures—a systematic review. Dis Mon. 63(1), 5-23.
5. Berg AT., Shinnar S., Darefsky AS., 1997. Predictors of recurrent febrile seizures. A prospective cohort study. Arch Pediatr Adolesc Med. 151(4), 371-378.
6. Saguil A., Servey J., 2020. Predicting the likelihood of a recurrent febrile seizure. Am Fam Physician. 101(8), 497-498.

7. Vezzani A., Granata T., 2005. Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia. 46(11), 1724–1743.

8. Okumura A., Uemura N., Suzuki M., 2004. Unconsciousness and delirious behavior in children with febrile seizures. Pediatr Neurol. 30(5), 316–319.

9. Sadleir L.G., Scheffer IE., 2007. Febrile seizures. BMJ. 334(7588), 307–311.

10. Byeon J.H., Kim G.H., Eun B.L., 2018. Prevalence, incidence, and recurrence of febrile seizures in Korean children based on national registry data. J Clin Neurol. 14(1), 43-47.

11. Kazemi A., Shervin Badv R., Fallah R., et al., 2021. The first febrile seizure; predisposing factors and recurrence rate. Iran J Child Neurol. 15(2), 69-76.

12. Dreier J.W., Li J., Sun Y., Christensen J., 2019. Evaluation of long-term risk of epilepsy, psychiatric disorders, and mortality among children with recurrent febrile seizures: A national cohort study in Denmark. JAMA Pediatr. 173(12), 1164–1170.

13. Kumar N., Midha T., Rao Y.K., 2019. Risk factors of recurrence of febrile seizures in children in a tertiary care hospital in Kanpur: A one-year follow-up study. Ann Indian Acad Neurol. 22(1), 31-36.

14. Alwan Y.F., Hussein H.J., 2013. Risk factors for recurrent febrile convulsion in children. KCMJ. 9(2), 14-16.

15. Kantamalee W., Katanyuwong K., Louthrenoo O., 2017. Clinical characteristics of febrile seizures and risk factors of its recurrence in Chiang Mai University Hospital. Neurol Asia. 22(3), 203-208.

16. Civan A.B., Ekici A., Havali C., 2022. Evaluation of the risk factors for recurrence and the development of epilepsy in patients with febrile seizure. Arq Neuropsiquiatr. 80(8), 779-785.

17. Pavlidou E., Tzitiridou M., Kontopoulos E., 2008. Which factors determine febrile seizure recurrence? A prospective study. Brain Dev. 30(1), 7-13.

18. Hartfield D.S., Tan J., Yager J.Y., 2009. The association between iron deficiency and febrile seizures in childhood. Clin Pediatr (Phila). 48, 420–426;

19. Vaswani R.K., Dharaskar P.G., Kulkarni S., Ghosh K., 2010. Iron deficiency as a risk factor for first febrile seizure. Indian Pediatr. 47, 437–439.

20. Hesdorffer D.C., Shinnar S., Lax DN., 2016. Risk factors for subsequent febrile seizures in the FEBSTAT study. Epilepsia. 57, 1042–1047.

21. Habib Z., Akram S., Ibrahim S., Hasan B., 2003. Febrile seizures: Factors affecting risk of recurrence in Pakistani children presenting at the Aga Khan University Hospital. J Pak Med Assoc. 53(1), 11-17.

22. Lubis S.N., Menglikulov B., Shichiyakh R., Farrux Q., Khakimboy Ugli B.O., Karimbaevna T.M., Ulugbek K., Bakhtiyarovna S.Z., Khabiba J., Sapaev I., Jasur S., 2024. Temporal and spatial dynamics of bovine spongiform encephalopathy prevalence in Akmola Province, Kazakhstan: Implications for disease management and control. Caspian J Environ Sci. 22(2), 431-442. doi: 10.22124/cjes.2024.7734.

23. Ashjazadeh N., Kashani K., Sahraian A., Asadi-Pooya A.A., 2014. Frequency of depression and anxiety among patients with psychogenic non-epileptic seizures. Galen Med J. 3(4), e224. doi: 10.31661/gmj.v3i4.2.

24. Zhumakhanova R., Zhaparkulova N., Sharipova S., Orazbayeva N., Yeszhan B., Zhaksybay Z., Ossikbayeva S., Akhmetova A., Ursheeva B., 2024. Innovative achievements in the detection of synaptic plasticity and oxidative stress in mice: Precision imaging, improved biosensoring, and personalized interventions for neurological disorders. Caspian J Environ Sci. 22(3), 697-713. doi: 10.22124/cjes.2024.7916.

25. Nazarbaghi S., Eftekhari Z., 2024. Exploring herbal remedies for migraine: Insights from the medicinal plants of Northern Iran. PBP. 6(2), 8-14. Available at: http://pbp.medilam.ac.ir/article-1-237-en.html.