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Febrile Seizure in Hospital Based Childrens; A Case Control Study

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KEYWORDS
Febrile seizure, Global Health, neurological disease, children, micro nutrients Difficency

ABSTRACT:

Background : Febrile seizure (FS) or febrile convulsion (FC) is the most common neurological disease. It commonly occurs among children aged 6 months to 5 years, with the global incidence rate of 2 – 5 % .

Objective: The main objective of this case study to find prevalence among hospitalized children of a tertiary care teaching hospital

Methodology: This hospital-based, case-control study was conducted at the Department of Paediatrics of a tertiary care teaching hospital, R Statistical Software is used for this study for the; A & B Group.

Result and conclusions: In the current study, the incidence of IDA and ZD was higher in children with FC (cases) compared to children without FC (controls). ZD was found among 86% of the cases and IDA was found among 73% of the case, indicating that hypozincemia and IDA are predisposing factors to FS. Significantly higher number of children in cases had lower serum ferritin levels (Iron deficiency) compared to control. As RDW can be used to distinguish between simple and complex type of seizure. Higher number of the children with FC had RDW of >15 compared to controls, indicating a possible relationship between RDW and FC. The final conclusion to this study is that deficiency of zinc and iron among children of 6 – 60 months is proposed as a modifiable risk element for FS. Early detection and timely correction of micronutrient deficiency (iron and zinc) might be helpful in preventing FS. However, long term randomized controlled trials with a large sample size are needed to make it as a treatment protocol.

INTRODUCTION

Febrile seizure (FS) or febrile convulsion (FC) is the most common neurological, age-dependent disorder associated with a temperature ≥ 38 ºC, without any evidence of intracranial infection or metabolic disturbance or previous history of a FS [1]. FC are caused by the atypical electric discharge inside the brain [2]. It commonly occurs among children aged 6 months to 5 years, with the global incidence rate of 2 – 5 % [3].

Generally, FC can be either simple or complex in nature. The FC having the potential for relapse is considered as simple FC [4] whereas the FCs that are prolonged (10 – 15 minutes) occurring more than once in a day are considered as complex FC [5]. Normally, FCs are not considered as epilepsy, but epilepsy can have FCs as foremost presentation. However, prediction of evolution of epilepsy after detecting occurrence of FC is certainly impossible. According to the published reports, consequences of a prolonged or recurrent FCs were found to be associated with increased risk of subsequent epilepsy [4,5] Several theories have been proposed to describe the pathophysiology of FCs, including genetic predisposition [6], infections [6], electrolyte disturbance [7], circulating toxins association [8] and interleukins [8], and microelement deficiency

Journal of Chemical Health Risks
www.jchr.org
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[9],and yet, pathophysiology of FC remains unclear. Published reports highlight that zinc, iron, selenium, copper, and magnesium play a significant role in FCs [10]. Zinc is a micronutrient that is crucial for the normal functioning of the central nervous system. It is required to synthesize gamma-amino butyric acid, an inhibitory neurotransmitter, which counteracts the inhibitory effects of calcium on the excitatory N-methyl-D-aspartate [11]. When a person has low zinc levels, N-methyl-D-aspartate receptors become activated and induce an epileptic discharge in children with high fevers [1]. Some researchers have described the possible role of zinc deficiency (ZD) in provoking FS [12-14]. However, Garty et al., reported that there was no relation between FS and cerebrospinal fluid zinc level [15]. A few researchers reported that iron deficiency (ID) stimulates the function of neurons and subsequently, rises the risk of convulsions [16]. It is well known that iron acts as a cofactor for synthesis of several enzymes in the body and it also has a role in the production and functioning of neurotransmitters. It is also useful in deoxyribonucleic acid (DNA) duplication and functioning of hormones [17]. Although, several researchers attempted to evaluate the connection between micronutrient deficiency (iron and zinc) and FS among children [13,16,18]. results were feeble or controversial. Hence, this study was conducted to find an association of FS with iron and ZD among children.

Methodology

Study Design: This hospital-based, case-control study was conducted at the Department of Paediatrics of a tertiary care teaching hospital. The study was executed during the period of November 2016 to May 2018, after receiving approval from the Institutional ethics committee.

Study Subjects and Selection Criteria:

A total of 104 children, aged 6–60 months, and presented to the pediatric department with febrile illness (temperature > 38 ºC/100.4 ºF) were involved in the study. The sample size was calculated using the standard formula. [19] Among 104 children, 52 children without FS were considered for the control group (Group A), and an equivalent proportion of children FS (either simple or complex), who matches with the selection criteria were considered for case group (Group B). Children with structural brain damage, central nervous system infection, history of a FS, chronic systemic disease (cardiac, renal, metabolic, malignancy, and/or rheumatologic), and neurodevelopmental delay were excepted from the study clinically.

FCs have been defined as a simple FS when the seizures are associated with fever, not recurrent within a 24-hour period and lasts for <15 minutes whereas, seizures of more than 15 minute-duration and happening more than once in 24 hours were considered as a complex FS [20].

Study Procedure

Sociodemographic and medical data including a detailed history of the child with specific reference to seizures and birth history was collected for all the children, after obtaining informed consent from their parents or legal guardian. Later, a detailed examination of the child was performed. All the details were recorded on a specially designed proforma.

Later, a venous blood sample (3 mL) was taken from all children in both groups (controls and cases) to measure hemoglobin (Hb) level, erythrocyte sedimentation rate (ESR), red cell distribution width (RDW), peripheral smear (PS), serum ferritin (SF) level, serum iron (SI) and serum zinc (SZ) level.

In general, diagnosis of ID mainly relies on SF levels. ID was diagnosed by hematologic investigations of serum ferritin < 12 ng/mL under normal ESR or < 30 ng/mL in the presence of raised ESR, or serum iron levels < 22 µg/dL [21,22].

Iron deficiency anemia (IDA) was defined by Hb<11gm/dL, SF levels< 12 ng/mL under normal ESR or < 30 ng/mL in the presence of raised ESR or serum iron levels < 22 µg/dL, and RDW > 15 % (World Health Organization, WHO), and peripheral smear showing microcytic hypochromic anemia or normocytic hypochromic anemia [22]. According to WHO recommendations, the SZ value < 65 µg/dL was considered for diagnosis of ZD (hypozincemia) [23].

Statistical analysis

Statistical analysis was done using R v386 3.5.1. The continuous variables (e.g. Hb, iron, zinc) were summarized as mean ± SD and related among cases and controls with independent t-tests. Categorical variables were compared using Chi-square ($\chi 2$) test. Further, logistic regression was performed to determine association of hematology data with recurrence. *P* value ≤ 0.05 considered as statistically significant.

Results

A total of 104 children participated in the current study with a male: female ratio of 1: 0.44 in both cases as well as the control group (Table 1).

Journal of Chemical Health Risks
www.jchr.org
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Table 1: Comparison of Socio-demographic Details and Clinical Characteristics of Children

Characteristics	Cases Fever with FC	Controls Fever without FC	*P* value
Gender			
Male	36	36	1
Female	16	16	
Age (months)			
<12	11	11	0.975
13–24	25	27	
25–36	7	7	
37–48	6	4	
49–60	3		
Seizure type			
Simple	40	0	N.A.
Complex	12	0	
Time gap between fever and seizure (hours)			
<24	34	0	NA
24-72	18	0	
Nature of febrile illness			
URTI	4	4	1
LRTI	29	29	
Acute GE	16	16	
UTI	3	3	
Family history of febrile seizures			
Yes	11	3	0.02*
No	41	49	
History of similar episodes			
Yes	15	0	< 0.01 *
No	37	52	
Natal history			
Normal	34	45	0.04 *
LBW	7	3	
LBW+ PT	11	4	
Child nutrition			
Normal	21	19	0.5
WHO grade 1	26	24	
WHO grade 2	5	9	

FC: Febrile Seizure; URTI:Upper Respiratory Tract Infection; LRTI:Lower Respiratory Tract Infection Acute GE: Acute gastroenteritis; UTI: Urinary Tract Infection; LBW: Low Birth Weight; LBW+PT: Low Birth Weight Pre-Term *: statistically significant; WHO: World Health Organization; NA: Not applicable Comparison of socio-demographic and medical characteristics between cases and controls were presented in Table 1. In this study, majority of the children (76.92 %) had a simple seizure. The time gap between fever and seizure was < 24 hours in majority of the cases (65.38). Further, a history of similar episodes of seizures in the past was reported by 28.85 % of the children. According to the study results, a significant difference was observed between cases and controls with regard to family history of seizures ($P < 0.01$), history of similar episodes of seizures ($P < 0.05$) and natal history ($P < 0.05$).

Journal of Chemical Health Risks
www.jchr.org
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Table 2: Comparision of Laboratory Investigations Between Cases and Controls

Laboratory Investigations	Cases Fever with Febrile seizures	Controls Fever without Febrile seizures	*P* value
Hemoglobin (g/dL) (n)			
< 11	48	21	< 0.001 *
≥ 11	4	31	
Red cell Distribution Width (%)			
< 15	15	29	0.005 *
> 15	37	23	
Ferritin (n) ng/ml			
< 12 - Normal ESR	2	0	0.002*
> 12 - Normal ESR	20	17	
< 30 - High ESR	11	1	
> 30 - High ESR	19	34	
ESR			
Normal	22	17	0.31
High	30	35	
Peripheral smear			
Microcytic hypochromic	35	10	< 0.01 *
Normocytic hypochromic	15	16	
Normal	2	26	
Iron deficiency anemia			
Yes	38	24	0.005 *
No	14	28	
Zinc deficiency (n)			
Yes (<65)	44	13	< 0.001 *
No (≥65)	8	39	
Iron deficiency			
Yes (< 22)	13	7	0.135
No (>=22)	39	45	

ESR: Erythrocyte Sedimentation Rate; *: Significance

Table 2 compares laboratory characteristics between cases and controls. According to the results, a significant difference exists between the controls and cases with reverence to the parameters, Hb ($P < 0.001$), RDW ($P = 0.005$), ferritin ($P < 0.004$), PS ($P < 0.01$), iron deficiency anemia (IDA, $P = 0.005$) and ZD ($P < 0.001$).With regards to the hematological profile, a significantly greater number of the children in cases had RDW of > 15 %, compared to controls. Peripheral smear studies revealed a significantly greater number of children with a microcytic hypochromic picture in cases as compared to controls ($P < 0.001$). ZD was found in 84.6 % of the cases, whereas IDA was found in 73 % of the cases.

Table 3: Comparison of Hemoglobin, Serum Zinc and Serum Iron Between Cases and Controls (t-test)

Parameters	Cases FC with Fever	Controls Fever without FC	*P* value
Hemoglobin in g/dL (Mean ± SD)			
< 11	8.99 ± 1.14	9.80 ± 0.95	0.001*
≥11	11.43 ± 0.40	11.98 ± 1.29	0.19
Total	9.18 ±1.29	11.09 ±1.6	<0.01*

Journal of Chemical Health Risks
www.jchr.org
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Serum Zinc in µg/dL (Mean ± SD)			
< 65	29.03 ± 10.94	57.18 ± 5.31	< 0.05 *
≥ 65	81.87 ± 9.31	81.95 ± 11.91	0.98
Total	37.16 ±22.08	75.76 ±15.26	<0.01
Serum Iron in µg/dL (Mean ± SD)			
< 22	14.08 ± 3.93	16.14 ± 3.04	0.22
≥22	64.10 ± 43.58	69.60 ± 41.98	0.57
Total	51.6±43.98	62.40±43.54	0.21
Ferritin (n) ng/ml (Mean ± SD)			
< 12 - Normal ESR	10.47±1.41	0	NA
> 12 - Normal ESR	23.05±4.91	61.35±31.70	<.001
< 30 - High ESR	22.33±6.80	16.61	NA
> 30 - High ESR	83.37±52.20	110.28±78.27	0.14
Total	92.49±70.19	44.45±43.30	<.001

FC: Febrile Seizure; ESR: Erythrocyte Sedimentation Rate; *: significance

Table 3 compares laboratory parameters Hb, SZ, SI and Ferritin level in cases and controls, indicating a substantial difference between the groups with the Hb levels < 11 g/dL ($P = 0.001$), and the zinc levels < 65 µg/dL ($P < 0.05$).

Table 4: Hematology Data of Controls and Cases

Hematology Data	Controls (N = 52)	Cases (N = 52)	
	Fever without seizures Mean ± SD	**Simple febrile seizures (N = 40) Mean ± SD**	**Complex febrile seizures (N = 12) Mean ± SD**
Hemoglobin g/dL	11.09 ± 1.60	9.26 ± 1.30	8.90 ± 1.16
Ferritin ng/ml	92.49 ± 70.19	46.65 ± 45.99	37.13 ± 31.99
Iron µg/Dl	62.40 ± 43.54	51.90 ± 47.62	50.58 ± 25.75
Zinc µg/Dl	75.76 ± 15.26	39.29 ± 22.42	30.06 ± 18.19

As revealed in Table 4, the hematological parameters were very low among cases when compared with controls. Also, all the hematological parameters were lower in complex FS compared to simple FS.

Table 5: Hematology Data Among Cases with History of Seizures and Without History of Seizures

Factors	History of seizures (N = 15)	No History of Seizures (N = 37)
Family history of FC	3 (20 %)	8 (21.62 %)
Complex FC	4 (26.66 %)	8 (21.62 %)
Hemoglobin (< 11 g/dL)	15 (100 %)	33 (89.19 %)
Ferritin (< 30 ng/ml)	9 (60 %)	23 (62.16 %)
Zinc (< 65 µg/dL)	13 (86.66 %)	31 (83.78 %)
Iron (< 22 µg/dL)	5 (33.33 %)	8 (21.62 %)
Iron deficiency anemia	10 (66.66 %)	28 (75.67 %)

Journal of Chemical Health Risks
www.jchr.org
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Table 5 indicates that children with a history of seizures have more complex FS, with Hb < 11 g/dL, zinc < 65 µg/dL and iron < 22 µg/dL.

Table 6: Univariate Logistic Regression Analysis of Factors Predisposing to Febrile Seizures

Factors	Odds Ratio	95% CI	*P* value
Family history of FC	0.5858	0.1129–3.0396	0.54
Complex FC	1.61	0.3419–7.60	0.18
Hemoglobin	< 0.0001	0-inf	0.99
Ferritin	1.2798	0.3080–5.3176	0.73
Iron	0.7077	0.1543–3.2466	0.65
Zinc	0.6875	0.1139–4.1509	0.68

In univariate logistic regression, the odds ratio values for family history of FC, complex FC, ferritin, iron and zinc were found to be 0.585, 1.61, 1.27, 0.707, and 0.687 respectively. However, they are not associated as a predisposing factors for the cases with history of febrile seizures ($P > 0.05$, Table 6).

Discussion

FS is a common problem found in young children. Although the pathogenesis is controversial, studies have exposed that the family background, genetic factors, immunologic disorders, vaccination, natal factors, ZD and ID may play a role in the development of FS [6,10]. In the current study, the incidence of IDA and ZD was higher in children with FC (cases) compared to children without FC (controls). These results are in agreement with the established studies [13-16,18]. However, in a few studies, IDA and ZD were less common and did not have an influencing role in FS [24-27]. In this study, the hematological parameters, namely, Hb, ferritin, iron, and zinc were lesser in complex FC, compared to simple FC cases and controls. This was in accordance with the other studies, which reported reduced Hb, ferritin, SI, and zinc among febrile children [13-16,18,27].

In the current study, ZD was found among 86 % of the cases and IDA was found among 73 %of the case, indicating that hypozincemia and IDA are predisposing factors to FS. Significantly higher number of children in cases had lower serum ferritin levels **(Iron deficiency)** compared to control (25% vs 1.92% p<0.001) The ZD findings were in line with the results of Mollah et al [13]. (2008) and Rabbani et al [14]. (2013) and the IDA results agreed with the previous studies reporting the role of ID in FS [5,16,18]. Recently, Gatto et al [23]. (2015) have reported that the occurrence of simple FS may increase if hypozincemia is associated with other risk factors, indicating a possible correlation between the mean SZ level and simple FS.

According to the established reports, RDW can be empirically used to distinguish between the simple and complex types of seizures [28]. Kartal and Kartal (2015), publicized that RDW might increase in certain circumstances such as iron deficiency, vitamin deficiency and anemia [29]. Eroglu et al., (2017), has reported increased RDW among complex seizures [30]. In this study, a significantly higher number of the children with FC had RDW of > 15 compared to controls, indicating a possible relationship between RDW and FC.

Thus, the higher incidence of IDA and ZD in children with FC suggests that low serum zinc and iron levels can serve as cofounding risk factors for FS.

Conclusion

Deficiency of zinc and iron among children of 6 – 60 months is proposed as a modifiable risk element for FS. Early detection and timely correction of micronutrient deficiency (iron and zinc) might be helpful in preventing FS. However, long term randomized controlled trials with a large sample size are needed to make it as a treatment protocol.

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Journal of Chemical Health Risks

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