Research Article

Association of Simple Febrile Seizure with Iron Deficiency Anemia in Children: A Case Control Study

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Abstract: Background: Febrile seizure is an established entity in Pediatrics which characterizes with absence of any intracranial infection or metabolic disorders. Simple febrile seizure carries a favorable prognosis without any sequelae. Still, it emerges as the most common etiology of seizure till the age of five years. Iron deficiency anemia is a commonly witnessed micro-nutrient deficiency with a worldwide distribution.

Objective: To establish relation of simple febrile seizure with iron deficiency anemia in paediatric population.

Materials and Methods: Case-control study, conducted in Pediatric Medicine Department, King Fahad Armed Forces Hospital Southern Region, Khamis Mushayat, Kingdom of Saudi Arabia, from1st January 2022 to 30th June 2023. The 102 children, having age six months to five years, with a diagnosis of first simple febrile seizure were assessed. Likewise, the control group included 102 febrile children without convulsion. The hematological parameters evaluated for diagnosis of iron deficiency anemia included hemoglobin, mean corpuscular volume, serum ferritin, serum iron, total iron binding capacity & red cell distribution width.

Result: The mean age for first simple febrile seizure was 23 months. Acute respiratory infection was the most common etiology (80%). Iron deficiency anemia was identified in 17% of cases of simple febrile seizure, in contrary to 6% of cases with febrile illness without seizure, with odds ratio of 3.2.

Conclusion: This study demonstrated that the children with iron deficiency anemia are at significantly higher risk of having febrile convulsions compare to control group with fever but without anemia.

Keywords: Fever, Febrile seizure, Iron Deficiency anemia, Serum ferritin, Hemoglobin, Convulsion, Mean corpuscular hemoglobin.

INTRODUCTION

Fever is routinely encountered in our clinical practice that characterizes during various infectious processes. On one end, it antagonizes the invading microorganisms and modulates the immune responses, while on the other side it can trigger a febrile seizure [1]. A febrile seizure is an established entity in Pediatrics which entails a convulsive event consorted with fever but without any intracranial infection or metabolic disorders or other defined cause [2]. Febrile seizure is considered as a commonly encountered neurologic disorder of infants and young children. It is indeed the most common etiology of seizure till the age of five years [3]. Simple febrile seizure carries a favorable prognosis without any sequelae [4]. Iron deficiency anemia is commonly witnessed micro-nutrient deficiency with a worldwide distribution, with a reported prevalence of 1-15% in the USA [5, 6].

Febrile seizure is an age-dependent phenomenon, with a documented incidence of 2 to 4% in children less than five years of age [7]. 70-75% febrile seizures are categorized under simple, while remaining as complex [8]. In-spite being characterized as a benign phenomenon, it results in a very frightening experience for the family and noticeable anxiety [9]. Therefore, it necessitates identifying various preventable risk factors, while avoiding unjustified interventions in such patients. Iron is cardinal for enzymes implicated in neurochemical processes, like myelin synthesis, neurotransmitter metabolism and brain energy metabolism [10]. Published research work pertaining to link febrile seizures with iron deficiency anemia have been inconsistent; certain studies showed that iron deficiency with or without anemia was more prevalent in children with febrile convulsions, while others exhibited no correlation [11-13]. Various systematic reviews and meta-analyses have pointed towards the association between them in the population aged three months to six years [13].

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Here, in southern region of Kingdom of Saudi Arabia, we studied the iron deficiency anemia in children with febrile seizures and controls in order to ascertain any relation between them,

MATERIALS AND METHODS

Case control study was carried out in Pediatric Department of King Fahad Armed Forces Hospital, Southern Region, Khamis Mushayat, Kingdom of Saudi Arabia in children with age six months to five years from 1st January 2022 to 30th June 2023 after due permission from local Research Ethics Committee (REC certificate number AFHSRMREC/2022/Pediatrics/637). From emergency department, 102 cases were enrolled in each of the two groups: simple febrile seizure and fever without convulsion. Studied individuals were earmarked by non-probability consecutive sampling. The aim of the study was to ascertain any relation, if any, of iron deficiency anemia with febrile seizures.

The first group consisted of children with normal development, aged six months to five years, who presented to the emergency department with first episode of simple febrile seizure. Patients were investigated for electrolytes imbalance (sodium, calcium) or hypoglycemia. Children with central nervous system infections, and history of epilepsy were excluded.

For control group, children with identical age were considered who were recognized to have a similar febrile illness, but not having a convulsion. The aim and the discretionary type of the study were highlighted to the parents for consent. Detailed history, especially age, gender, associated symptoms, and family history, was sought in each case through an interviewed questionnaire. Temperature was recorded with infrared thermometer.

Iron deficiency anemia was defined while utilizing World Health Organization (WHO) criteria for age with hemoglobin (Hb) <11.5 g/dL (<10.5 g/dL in cases aged till 2 years), mean corpuscular hemoglobin (MCH) <26 pg (normal range 26-32 pg), mean corpuscular volume (MCV) <70 fL (normal range 70-96 fL), red cell distribution width (RDW) >15% (normal range 11.5-14.5%), decrease red blood cell mass (normal range 4.06-5.30 × 106/µL), serum ferritin <30 ng/mL (normal range 30-400 ng/ml), total iron binding capacity (TIBC) >450 µg/dL and serum iron <60 µg/dL [14].

STATISTICAL ANALYSIS

The data was analytically evaluated using descriptive statistics, including frequency, percentage, standard deviation and mean, as well as analytical statistics like Chi Square test and T-test to compare various variables. P value ≤0.05 was taken as significant. Odds ratio was calculated.

RESULT

A total of 204 children were enrolled into the study. Among them, 102 children were having the diagnosis of first simple febrile seizure, while the control group included 102 febrile children without convulsion. Among studied groups, the mean age was 23.8 ± 16.9 months. Gender distribution in both groups was identical with 50.4% being males and 49.6% females.

The commonest etiology of fever was acute respiratory infection in both groups with 81 (80%) and 78 (77%) in the case and control groups respectively. Acute gastroenteritis was the next identified cause, as recognized in 15 (15%) patients in case and 17 (17%) in the control group. It was followed by urinary tract infection in two patients (2%) in either group.

Iron deficiency anemia was seen in 17 patients (17%) out of the 102 children with simple febrile seizure. In contrary, only six patients (5.8%) in control group were having iron deficiency anemia with p-value of 0.0001 which is highly significant (Tables **1**, **2**). Odds ratio turned out to be 3.2, revealing that the children with iron deficiency anemia were 3.2 times more likely to have a febrile seizure than the children without iron deficiency anemia.

Table 1. Frequency Distribution of Iron Deficiency Anemia among the Studied Groups (n=204).

Iron Deficiency Anemia	No. of Patients		p-value
	Group A (Febrile seizures) (n=102)	Group B (Control) (n=102)	
Yes	17 (17%)	6 (5.8%)	0.0001
No	85 (85%)	96 (94.2%)	
Total	102	102	

Table 2. Demographic Characteristics of Children under Study (N=204).

Characteristics		No. of patients		p-value
		Group A (Febrile seizures) (n=102)	Group B (Control) (n=102)	
Age (months)		23.8 ± 16.9	22.9 ± 15.6	0.912
Gender	Boy	50	53	0.417
	Girl	52	49	

The mean hemoglobin among the group A with febrile seizures was noted to be 12.39 ± 1.25 g/dL. The documented mean hemoglobin in group B was better as depicted by value of 12.81 ± 1.41 g/dL. Among the iron deficiency anemia cases, mean serum ferritin was 33.99 ± 9.83 ng/mL in group A and 36.77 ± 8.84 ng/ml in group B as exhibited in Table **3**.

Table 3. Various Indices of Iron Deficiency Anemia among the Studied Groups (n=204).

Indices	No. of patients		p-value
	Group A (Febrile seizures) (n=102)	Group B (Control) (n=102)	
Iron Deficiency Anemia	17 (17%)	6 (5.8%)	0.0001
Mean Hemoglobin (g/dL)	12.39 ± 1.25	12.81 ± 1.41	0.553
Mean Corpuscular Volume (fL)	78.05 ± 10.62	79.72 ± 11.20	0.104
Red Cell Distribution Width (%)	13.71 ± 1.54	13.37 ± 1.65	0.530
Serum Ferritin (ng/mL)	33.99 ± 9.83	36.77 ± 8.84	0.363
Total Iron Binding Capacity (µg/dL)	371.43 ± 76.73	348.78 ± 73.98	0.021
Serum Iron (µg/dL)	112.88 ± 36.16	124.24 ± 33.74	0.014

DISCUSSION

Iron is an essential element in the body with an established role in growth and development in pediatric age group [15]. Neurological disorders inferring from deficiency of iron include neurodevelopmental delay, cyanotic breath holding spells, increased intracranial hypertension and varying cognition issues [16, 17]. Iron deficiency has been linked with febrile seizure in literature [18]. We carried out this study to ascertain iron deficiency anemia as a risk factor for febrile seizures in less than five years age.

Among the studied groups, the mean age was 23.8 ± 16.9 months. Kumar *et al*. had reported mean age of febrile seizure as 18 months [8]. Jang *et al*. documented mean age of 27.1 ± 13.5 months [4].

Our study revealed no gender biased among the children with febrile seizures (50.4% being males vs 49.6% females). Jang *et al*. had published a slight male preponderance as involved cases were 55.6% male [8].

The commonest etiology identified for febrile seizure in our study was acute respiratory infection (80%), followed by acute gastroenteritis in 15%. Respiratory illness was the cause behind the illness in 75% of studied subjects by Jang *et al*. [8].

Our results exhibited febrile seizures being more prevalent in iron deficiency anemia in contrast to the control group, with odds ratio of 3.2. The study conducted by Naveed-Ur-Rehman and Billoo also revealed iron deficiency anemia was associated with higher risk of febrile seizures as compared to control group [14]. Similar results were found in research conducted in different countries depicting their association [15, 18]. While utilizing meta-analysis, Kwak BO, *et al*. and Idro R, *et al*. had positively established the link between febrile seizures and iron deficiency anemia (diagnosis based on plasma ferritin) [9, 19]. In the meta-analysis of Kwak BO, *et al*. the linkage between the iron deficiency anemia and febrile seizures was ascertained among children aged between three months to six years [9].

Moreover, our study showed prevalence of iron deficiency anemia in 17% cases with simple febrile seizure. Kwak BO, *et al*. while performing the meta-analysis of 17 studies, with enrolling 2416 children with febrile seizures and 2387 controls, exhibited iron deficiency anaemia contributing as a significant risk factor for febrile seizures [9]. Kumar BT, *et al*. documented similar results [8]. Addil F, *et al*. noticed iron deficiency anemia in more than half patients of febrile seizures [20]. Kumari PL, *et al*. in India observed iron deficiency in 63% of patients with febrile seizures [21]. Results of the above studies were consistent with our observations. Iron deficiency anemia was recognized in 24% of febrile seizures in the region of Iraq [22]. A Canadian study exhibited febrile seizures being twice likely in children with iron deficiency (plasma ferritin level ≤30 ng/dL) but without any association of anemia in studied population [23]. Likewise, Sharif MR, *et al*. has given similar association cases with febrile convulsion, as compared to the controls [24]. However, Bidabadi E, *et al*. has presented contradictory results as iron deficiency anemia was less frequent among the febrile seizure cases [25].

All this reflects the relation of simple febrile seizures with iron deficiency anemia. However, our study has not evaluated the frequency of febrile seizures once iron deficiency anemia has been corrected in such patients. Hence, further research efforts can steer us in uncovering the role of iron supplementation in averting such events in high risk patients.

CONCLUSION

Our study showed higher prevalence of iron deficiency anemia in children with simple febrile seizure as compared to the febrile children without any convulsion. The results of multiple studies performed before and combined data in meta-analysis also exhibited identical outcome in younger preschool children. It can be inferred that iron deficiency anemia can serve as modifiable risk factor for the febrile seizures. Moreover, the interventions aimed towards diagnosing and treatment of iron-deficiency anemia in individuals with febrile seizures can avert such events in future.

AUTHORS' CONTRIBUTION

- **Muhammad Saeed**: Study Design, Proof reading.
- **Mohammad Hassan Hussain Al Sumaili**: Study Question-

naire, Critical Revision.

- **Badriah Gharamah Al Asmari**: Conception, Literature Search.
- **Mahnoor Saeed and Asma Imtiaz Hotiana**: Drafting.
- **Ali Mujtaba Tahir**: Data Analysis, Drafting.
- **Awad Salem Alrashdi and Saad Mufarrih Al Abdullah**: Data Collection.
- **Ali Maqbool**: Literature Search.
- **Abdul Qadir**: Data Analysis.

CONFLICT OF INTEREST

Declared none.

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