Original Article

The risk associated with iron deficiency anemia for simple febrile seizures in children: A case–control study

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ABSTRACT

Background: Studies have postulated iron deficiency state to be a risk factor for febrile convulsions as it changes the threshold of neurons excitation which may lower the threshold for seizures in children. However, many other studies have reported a protective role for febrile convulsions by increasing the neuronal threshold. **Objective:** The objective of the study was to evaluate the association of iron deficiency anemia (IDA) as a risk factor for the occurrence of simple febrile seizures (FS) in children. **Material and Methods:** A case-control study was conducted in a tertiary teaching hospital from September 2015 to February 2017. A total of 240 cases with fever and simple FS were enrolled according to the inclusion and exclusion criteria. Another 100 cases of children without seizure but with short duration of fever were enrolled as controls. Blood samples were then taken for assessing the hematological indices of these patients. The results were statistically analyzed. **Results:** Incidence of IDA was found to be more in children with simple FS than controls but was not statistically significant (p=0.35). Furthermore, no association was found with other hematological indices with FS occurrence. **Conclusion:** We could not find any association of IDA as a risk factor for a simple FS.

Key words: *Anemia, Febrile seizures, Ferritin, Iron deficiency*

Febrile seizures (FS) are the commonest types of seizures occurring in children with a prevalence of 5% in all children [1]. Their incidence in India is 10–17% which is higher than in developed countries (2–7%) [2]. FS are defined as seizures that occur between the age of 6 and 60 months with a temperature of 38°C (100.4°F) or higher that are not the result of central nervous system (CNS) infection or metabolic imbalance and occur in the absence of a prior history of FS [3]. The link between fever and seizure activity is suggested by animal studies to a possible role of endogenous pyrogens like interleukin 1β that increases neuronal excitability [4].

Majority of the FS are simple and are considered benign, but a small subset may develop recurrent FS and even lesser may develop epilepsy. These FS are life-threatening events with a risk of aspiration and are traumatizing to the child and parents while also imposing extra health care costs on the family. Recurrence of FS varies between 25% and 40% based on the number of risk factors involved [5]. Hence, various studies have been carried out to identify correctable risk factors to reduce the prevalence of FS.

Iron deficiency is the most common micronutrient deficiency worldwide, leading to iron deficiency anemia (IDA) which affects one-third of the children under 4 years [6]. Iron is needed for the metabolism of brain energy, neurotransmitters, and the production of myelin for nerve cells. Iron deficiency state can change the amplitude and threshold of neurons excitation which may lower the seizure threshold in children and thus iron deficiency has been postulated to be a risk factor for febrile convulsions [7-9]. Other studies have yielded completely conflicting results with findings of IDA in playing a protective role against febrile convulsion by increasing the threshold of neuron excitation [10-12]. Given these contradictory results and due to the high prevalence of these two conditions, we decided to study the association of IDA as a risk factor for simple FS.

MATERIALS AND METHODS

The study was conducted in the Department of Paediatrics of a teaching hospital in the Armed Forces from September 2015 to February 2017 after getting clearance from the Institutional Ethical Committee. Children who presented as simple FS to the emergency department or wards between the age group 6 and 60 months were enrolled for the study. The diagnostic criteria were based on the American Academy of Pediatrics clinical practice guidelines and included generalized seizures with fever of a short duration (<15 min) in the above age group, no recurrence of seizures within 24 h with the child otherwise neurologically

healthy, and without any neurological abnormality before and after the episode of seizures [3]. Children presenting with complex FS, afebrile seizures, with neurodevelopmental delay, signs of CNS infection, head injury, metabolic or electrolyte imbalance, previously diagnosed with anemia, on an iron supplement, or very sick children were excluded from the study.

The sample size was calculated with the formula n=4 (pq/L^2), where p=0.3 (occurrence of IDA in children with the 1st episode of FS as per previous studies), q=1−p, and L=allowable error. For the study, L was presumed to be 20% of p, giving a power of (1−L), i.e.,80% to study. Hence, n=4 $(0.3\times0.7/(0.2\times0.3)^2=233$. A total of 240 children of the above age group with fever and suffering from the first episode of simple FS were taken as cases and a total of 100 children suffering from a short duration of fever (<3 days) without seizures were taken as the control group.

After written informed consent, a detailed history and examination of the child were carried out. Blood samples were obtained in an ethylenediaminetetraacetic acid and a sterile container sent for evaluation of hemoglobin, red cell distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and MCH concentration (MCHC) using an automated hematology analyzer (LH 750, Beckman Coulter, US). Serum ferritin, total iron-binding capacity (TIBC), and serum iron samples were analyzed using the enzyme-linked immunosorbent assay method. As per the WHO criteria, IDA was diagnosed in the presence of hemoglobin <11 g%, RDW >15%, and serum ferritin <12 ng/L. Other values of MCV <72 fl, MCHC <32 g/dL, serum iron <50 µg/dL, and TIBC >450 µg/dL were considered abnormal.

The obtained results were entered into MS Excel. The data were analyzed using Epi Info software 3.5.4 version 2012. The association between parameters was studied using Pearson Chi-square test, Fisher's exact test, Student's t-test, and logistic regression at the appropriate level. The statistical significance of different parameters was calculated based on odds ratio with 95% confidence limit with p<0.05 was calculated as significant.

RESULTS

A total of 240 children between 6 and 60 months with simple FS were taken as cases and 100 children of the same age group were taken as the control group. The subjects were further subdivided into five groups based on their age (Table 1). The mean age for seizure in the case and control group was 27.28±13.88 and 32.80±16.85, respectively. There was no correlation of gender with FS and anemia and the difference in the ratio of boys and girls in two groups was also not statistically significant.

The results of blood indices in the case and control groups are listed in Table 2. Children with FS having anemia were 38.4%, which were higher than 33% of the children with anemia in the control group but did not reach statistical significance. There was also no statistical difference seen in HB, RDW, MCV, MCHC, serum ferritin, serum iron, and TIBC between the two groups.

Table 1: Distribution of age and sex in the study patients

Variable	Group	Cases=240, n (%)	Controls=100, n (%)
Age (months)	≤12	33 (13.80)	20 (20.00)
	13–24	100 (41.70)*	19 (19.00)
	25–36	54 (22.50)	16 (16.00)
	37–48	29 (12.10)	16 (16.00)
	>48	24 (10.00)	29 (29.00)
	Mean±SD	27.28±13.88	32.80±16.85
Sex*	Male	143 (59.6)	64 (64.00)
	Female	97 (40.4)	36 (36.00)

DISCUSSION

In the present study, the majority of cases (41.7%) of FS occurred in the 13–24 months age group. This is in accordance with the studies done by Kumari *et al.* and Kumar *et al.* [7,13]. FS is age-dependent and the age group of 12–24 months is regarded critical for developing FS. Although the mechanism of this increased susceptibility is unclear, animal models suggest that there is enhanced neuronal excitability during the normal brain maturation [4].

IDA is the most common type of anemia where cultural practices, habits, diet and socioeconomic conditions of the family have a major role in its prevention. Studies have suggested that the development of FS is associated with the socioeconomic status of the patient's family [14]. The present study was conducted in the children of the Armed Forces and there was no difference in the economic status of the families in these two groups studied. The incidence of anemia was 38.3% in the case group and 33% in the control group. These children had better medical facilities and socioeconomic status due to which the prevalence of anemia was lesser compared to the general population where it has been reported to be as high as 53% [6].

Studies by different workers on the relationship between IDA in FS have yielded conflicting results. The low occurrence of simple FS in children with IDA has been reported and it has been postulated that iron deficiency increased the threshold of neuron excitation and thus had some protective role against FS as reported by other authors [10-12]. Derakhshanfar *et al.* studied a large sample consisting of 1000 children (500 in each of the case and control groups) and concluded that the risk of febrile convulsion in children suffering from iron deficiency was less than in other children [10]. This was attributed to the role of iron in exciting neurotransmitters such as monoamine oxidase and aldehyde oxidase and thus its deficiency led to a reduction in the excitation power of the neurons and a decline in the probability of convulsion. Kobrinsky *et al.* concluded that IDA may be protective for the first febrile convulsion [11]. Talebian *et al.* also studied 120 children and reported that there was a decreased probability of the occurrence of convulsion in children afflicted with anemia [12].

Their results contradict those obtained in other studies which have suggested IDA of being a risk factor for simple FS as fever deteriorated the negative effect of anemia on the brain which

Table 2: Distribution of cases and control, according to other blood indices

Blood indices	Cases n (%)=240	Controls n (%)=100	Odds ratio (CI)	p-value
Hemoglobin				
Normal (≥11 g/dl)	148 (61.6)	67 (67)	OR: 1.26 (CI.772–2.063)	0.35
Anemia (<11 g/dl)	92 (38.4)	33 (33)		
Red cell distribution width				
Normal (<15%)	165 (68.8)	65 (65.0)	OR: 0.844 (0.515–1.382)	0.5
Abnormal (>15)	75 (31.2)	35 (35.0)		
Mean corpuscular volume				
Normal (72–90)	21 1 (87.9)	89 (89)	OR: 1.112 (0.532–2.324)	0.77
Abnormal (<72)	29 (12.1)	11 (11)		
MCHC				
Normal (32–36)	163 (67.9)	73 (73)	OR: 1.277 (0.76–2.144)	0.35
Abnormal (<32)	77 (32.1)	27 (27)		
Serum ferritin				
Normal (13–350)	151 (62.9)	69 (69)	OR: 1.31 (0.797–2.159)	0.28
Abnormal (<12)	89 (37.08)	31 (31)		
Serum iron				
Normal (50–150)	149 (62.1)	70 (70)	OR: 1.425 (0.863–2.352)	0.16
Abnormal (<50)	91 (37.9)	30 (30)		
Total iron-binding capacity				
Normal (250–450)	219 (91.3)	93 (93)	OR: 1.274 (0.524–3.099)	0.59
Abnormal (>450)	21 (8.8)	7 (7)		

then may cause seizures. In 1996, Pisacane *et al.* found anemia in 30% of the children with febrile convulsion while only 14% in the control group exhibited anemia [8]. These findings have been repeated in later studies carried out by Kumari *et al.* [7] and Daoud *et al.* [9]. Recently, Khan *et al.* in 2016 [15] reported FS to be twice as common in children having IDA as compared to those without it.

In our study, though seizures were more common in cases with anemia than controls, the difference was not significant. Moreover, no significant difference between the two groups was observed with respect to mean HB, RDW, MCV, and MCHC. Similar results were reported by Kunwar *et al.* in 2015 [16]. Daoud *et al.* also concluded that there was no statistically significant relationship between low hemoglobin, FS, and type of FS [9].

Serum ferritin is a nonspecific acute phase reactant that might increase in any inflammatory condition but a low level in the fever setting makes it more reliable. Daoud *et al.* reported a significant decrease in the ferritin levels in cases with FS [9] while Derakhshanfar *et al.* found increased levels in cases with FS compared to controls [10]. In our study, mean serum ferritin levels were 13.12±3.07 and 19.764±2.89 in case and controls, respectively, with a statistically insignificant p=0.028. Furthermore, our study showed low serum iron in FS children as compared to the control group, but it was not statistically significant (p=0.16). Kumari *et al.* and Derakhshanfar *et al.* concluded that poor iron status was an important risk factor for the first episode of the first FS [7,10].

The strength of our study included a large sample size, standardized criteria for diagnosing FS, and iron deficiency prevalence bias by the concurrent enrolment of controls and cases. The study had some limitations as it was a hospital-based study where the prevalence of exposure and outcome variables was different from a community setting.

CONCLUSION

In our study, we found that though the frequency of IDA with FS was more than controls, but this was not statistically significant to establish it as a risk factor for FS. Therefore, larger prospective interventional and follow-up studies should be undertaken to establish IDA as a modifiable risk factor and continued emphasis should be given on its screening and treatment in children to prevent their immediate and long-term outcomes.

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