

Iron deficiency as risk factor for febrile convulsion and the association of iron deficiency anemia and febrile convulsion



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ABSTRACT

Background: Febrile seizure occurs in 2–5% of neurologically healthy infants and children. The recurrence of febrile seizures is 30% after single episode, 50% after 2 or more episodes, and 50% when febrile seizures occur in infants. Their incidence of febrile seizures in India is 10–17% which is higher than in developed countries (2–7%). **Aims and Objectives:** The purpose of this study was to evaluate iron deficiency (ID) as a risk factor for febrile convulsion and the association of ID anemia with febrile convulsions. **Materials and Methods:** This was an observational case–control study conducted in tertiary care center in central India between December 2019 and June 2021. All patients with febrile seizures taken as cases and control from similar age group with febrile illness. Body temperature of children in both the groups was measured and recorded. The blood tests of complete blood count, serum iron, and TIBC were performed. **Results:** In the present study, mean age was 2.33 years in case and mean age was 2.204 years in control. The mean hemoglobin levels were 8.25 ± 1 g/dL in the febrile seizure case group and 9.86 ± 1.49 g/dL in the control group; and their statistical difference was significant. Serum ferritin values was significantly lower among cases group than the control group. The average of MCV, MCH, and MCHC for the case group was less than that of the control group. The present study also demonstrates an association between ID and febrile seizures. Thus, ID is one of the possible risk factors for febrile seizures. **Conclusion:** The present study showed that hemoglobin, MCV, serum ferritin, and serum iron levels are significantly lower in children suffering from febrile seizures, suggesting that a low iron status has an important role in children with febrile seizures. Thus, ID is predictor for febrile convulsion.

Key words: Children; Febrile seizure; Iron deficiency anemia

INTRODUCTION

Febrile seizures are defined as the seizures that occur between the age of 6 and 5 years during febrile illness with a temperature of 38°C (100.4°F) or higher, in the absence of central nervous system infection or any metabolic imbalance and previous history of afebrile seizures.¹ Their incidence of febrile seizures in India is 10–17% which is higher than in developed countries (2–7%).²

Despite a concentrated effort by the World Health Organization (2014) to increase awareness and promote

iron supplementation, iron deficiency (ID) remains the most prevalent micronutrient deficiency, with the most severe form, ID anemia, affecting over 20% of pregnant women and 23% of children under the age of 5. Its effect on developing children is particularly devastating since iron supplementation later in life cannot remedy the learning difficulties, behavioral problems, and psychiatric disorders that are associated with the early life ID.^{3,4}

ID reduces the metabolism of some neurotransmitters, such as monoamine and aldehyde oxidase⁵, and thus, it may alter the seizure threshold of a child.⁶ In addition, the

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expression of cytochrome C oxidase, a marker of neuronal metabolic activity, is decreased in ID anemia.⁷ As ID and febrile seizures are common during early childhood, it was postulated that some association may exist between these two clinical conditions. To establish some correlation among them, various studies were undertaken with majority of the studies concluding that ID is common in febrile seizure patients,^{8,9} few studies concluded that iron status has no role in febrile seizures¹⁰ and a few studies concluded that ID raises seizure threshold; thereby, it protects children from seizures.¹¹

Hence, it could be possible that ID anemia may predispose to other neurological disturbances such as irritability and weak memory along with febrile seizures. The observed percentage of febrile seizures is 2–4% of all infants and that of recurrence in children with <1 year of age is around 50% and 28% for those older than 1 year of age.¹² Majority of the cases of febrile seizure are found to occur in age group 14–18 months which directly overlap with the age group of 6 months–24 months which have a maximum occurrence of ID anemia.^{13,14}

In view of high prevalence of ID in children <5 years of age in our country and conflicting results from the previous studies, we planned this research to study the role of ID as risk factor for febrile seizures in children. Therefore, the present study will help in reducing or preventing the occurrence of febrile seizures in community.

Aims and objectives

The purpose of this study was to evaluate iron deficiency as risk factor for febrile convulsion and the association of iron deficiency anemia and febrile convulsion.

MATERIALS AND METHODS

This is a case–control study, in which 60 children (6 months–5 year) presenting with the first episode of febrile seizure to the pediatric emergency departments of Dr. Panjabrao Deshmukh Medical College, Amravati between December 2019 and May 2021. Before start of the study, the Institutional Ethical Committee Approval (research protocol no.131-31126-191-223388) was taken.

In the present study, 12 patients with febrile seizures between the age of 6 and 5 years having history of high-grade fever, that is, above 100°F, without any organic cause of central nervous system were selected as cases. On the other hand, 48 patients having history of fever, but without any seizure's history, were selected as control

for study. Patients with history of seizures suspected CNS infection and patients who were Diphtheria, Pertussis, and Tetanus vaccinated up to 48 h were excluded from the study. Parents were asked to sign the consent form in all cases after the goals and voluntary nature of the study were explained to them. Parents were asked to fill out an interview questionnaire with personal information about their children, such as their age, gender, seizure history in the family, occupation, and socioeconomic status were noted. Body temperature of children in both the groups was also measured and recorded. The blood tests of complete blood count, serum iron, and TIBC were performed. Anemia is defined as hemoglobin level <11.5 g/dl, MCV<75 fl, MCH<25 pg, MCHC<31 g/dl, and RDW<14. The normal level of serum iron was determined as Fe>40 µg/dl for children younger than 1 year and Fe>50 for children over 1 year. The normal range of TIBC was considered 210–430 µg/dl. The normal transferrin saturation percentage was considered higher than 15%.^{15,16}

Statistical analysis

The data were coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. The data were examined using descriptive statistics including frequency, percentage, standard deviation, and mean as well as statistics such as Chi-square test, which were performed to compare qualitative variables; the analysis of variance test and student T-test performed to compare quantitative variables.

RESULTS

The study population consisted of 12 children in the febrile seizure case group and 48 children in the control group. The mean age in the febrile seizure cases group was 2.33±1.53 months and 2.20±1.06 months in the control group (P=0.73). We observed no significant differences in terms of age or gender between the two groups when comparing to demographic characteristics. The mean hemoglobin levels were 8.25±1.15 g/dL in the febrile seizure case group and 9.86±1.49 g/dL in the control group; and their statistical difference was significant. A comparison of the demographic and clinical characteristics between the two groups showed that, in the febrile seizure cases group, 7 (58.3%) out of 12 patients had PICA, whereas, in the control group, 20 (41.7%) out of 48 patients had PICA. In febrile seizure cases, 100% of the patients had pallor, while only 6 (12.5%) of the control group had the pallor condition. Among the cases only, 8 (66.7%) patients had hypochromic microcytic peripheral smears, while 4 (33.3%) patients

had normocytic peripheral smears. We observed that peripheral smear value was significantly lower among febrile seizure case group than control group, as shown in Table 1.

In our findings, the mean of serum ferritin level was 100.23 ± 35.44 $\mu\text{g}/\text{dl}$ in the febrile seizure case group and 154.83 ± 51.28 $\mu\text{g}/\text{dl}$ in the control group; this represents that serum ferritin values was significantly lower among cases group than the control group. The mean of TIBC in the febrile seizure case group was 349.55 ± 51.02 g/dl and 333.28 ± 37.93 g/dl in the control group; $P=0.22$ indicated that the TIBC value was statistically non-significant and higher in the case group than in the control group, whereas, the mean of serum transferrin in the febrile seizure case group was 231.98 ± 14.62 $\mu\text{g}/\text{dl}$ and 274.43 ± 47.22 in the control group. Similarly, the mean of serum iron among case group was 100.4 ± 26.06 and 120.29 ± 44.47 $\mu\text{g}/\text{dl}$ in the control group. It represents that serum iron value was significantly lower among case group as compared to control group.

The average of MCV, MCH, and MCHC for the case group was less than that of the control group. In the present study, we found that serum transferrin value was significantly lower among case group than control group. The average of Hb, serum ferritin, and serum

transferrin was statistically significant in two groups, whereas, we observed no difference in the proportion of cases between two group ($P>0.05$) in terms of TIBC, as shown in Table 2.

Below Graph 1 represent, four boys and eight girls were from (febrile seizure) case group and 30 boys and 18 girls were from control group. This represents, the incidence of febrile seizures was found higher in girls (66.7%) than in boys (33.3%) among both the groups.(Graph 1).

DISCUSSION

The present study was conducted in the Department of pediatrics Panjabrao Deshmukh Hospital and Research Center, Amravati, during the period of December 2019 –May 2021. The purpose of this study was to determine the association of ID anemia in Febrile seizure patient. In our findings, the peak incidence of febrile seizure occurs during 1–3 years of age (66.7%) and the mean age was 2.33 years. This is comparable to the previous studies. The peak age of onset being 14–18 months of age as per Nelson textbook of pediatrics.^{15,16} The peak incidence of FS was noted between 14 and 18 months as per Aicardi's epilepsy febrile convulsions guidelines.¹⁷ Berg et al., in their study, they reported, the peak incidence is between 18 and 24 months.

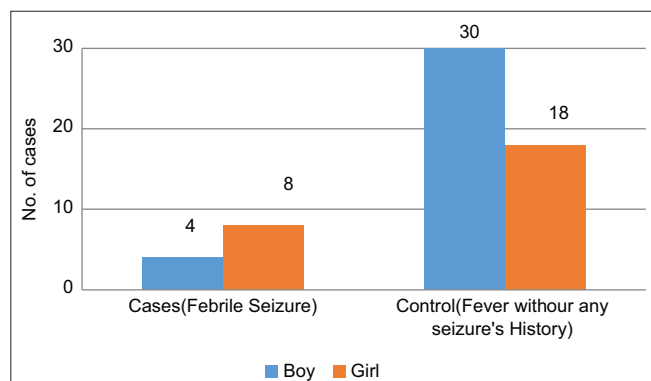
Table 1: Demographic data and clinical characteristics with case and control group

Personal information	Cases (Febrile Seizure)	Control (Fever without any seizure's History)	PV
Gender			
Boy	4	30	0.06
Girl	8	18	
Age (Yrs.)*	2.33 \pm 1.53	2.20 \pm 1.06	0.73
PICA			
Present	7	20	0.16
Absent	8	28	
Pallor			
Present	12	6	0.01
Absent	0	42	
Peripheral smear			
Hypochromic microcytic	8	21	0.15
Normocytic normochromic	4	27	

*Mean \pm Standard Deviation

Table 2: Mean and standard deviation of different indicated of ID anemia in children under study

Iron anemia A	Cases (Febrile Seizure)	Control (Fever without any seizure's History)	PV
Hb	8.25 \pm 1.15	9.86 \pm 1.49	0.003
Serum iron	100.4 \pm 26.06	120.29 \pm 44.47	0.01
TIBC	349.55 \pm 51.02	333.28 \pm 37.93	0.22
Serum transferrin	231.98 \pm 14.62	274.43 \pm 47.22	0.001
MCV	70.38 \pm 5.06	80.76 \pm 7.40	0.001
MCH	19.52 \pm 0.97	21.44 \pm 2.44	0.01
MCHC	32.90 \pm 1.27	33.20 \pm 1.19	0.44
Serum ferritin	100.23 \pm 35.44	154.83 \pm 51.28	0.001



Graph 1: Comparison of febrile seizure between case and control group

The present study depicts that the incidence of febrile seizures is slightly higher in girls (66.7%) than in boys (33.3%) among the case and the male: female ratio 1:2. Ratios of boys: girls in different studies have ranged from 1.1:1 to 2:1.¹⁶⁻²¹ However, our present study is in contrast to other large studies done by Verity et al.,²¹ 1985 who found that there is no sex difference in occurrence of febrile seizures.

In the present study, 8 (66.7%) patients have hypochromic microcytic peripheral smear and 4 (33.3%) patients have normocytic normochromic peripheral smear among cases only. In the study conducted by Nigade and Khambalkar (2018),¹⁹ patients with hypochromic microcytic peripheral smear are 114 which are about 67% and normocytic normochromic are 56 which are 33%.

In the present study, the mean serum ferritin level was 100.23 among case which was significantly lower than control group (154.83), whereas, Daoud et al., (2002)²⁰ in their study group from Jordan, found that the mean ferritin level was 29.5 ng/ml²², while Derakhshanfar et al., (2012)²³ found increased levels in cases with FS compared to controls. However, Bidabadi and Mashouf (2009)²² and Yousefichaijan et al., (2014)^{11,23} concluded that the mean value of serum ferritin for the case group was higher than that of the control group. It is probably due to the fact that ID anemia is more prevalent in our country; the mean serum ferritin level of Indian children is also low when compared to the Western standards. This finding comes in close agreement with other studies; Pisacane et al.,²⁴ Hartfield et al.,²⁵ and Vaswani et al.⁸

Our study demonstrated a statistically significant difference in the proportion of children with febrile seizures and shows that those children not only have low serum ferritin but also low hemoglobin and low mean corpuscular

volume. Daoud et al.,²⁰ in his study, found that a significant proportion of children with febrile seizures had only low serum ferritin level.

The mean MCV, MCH, and MCHC for the case group were less than that of the control group which is according to the results obtained by Shaikh et al., (2018)²⁶, Kamalammal and Balaji (2016).²⁷

Fallah et al., (2014)²⁸ from Iran showed low mean HB (11.46±1.18 gm/dL) in case group as compared to control group (11.9±0.89 g/dL) which was significant. In an Iranian study done in 2009 by Omran, MS showed mean hemoglobin 11.75±1.15 gm/dl in case group, while 11.99±1.94 gm/dl in control group, and this difference was not statistically significant.

The present study shows, the mean of serum ferritin level was 100.23±35.44 µg/dl in the febrile seizure case group and 154.83±51.28 µg/dl in the control group; this represents that serum ferritin values was significantly lower among cases group than the control group. Hence, it emphasized there were strong correlation between ID and febrile seizures. These findings were concordance with the studies done by Daoud et al., (2002)²⁰ Rehman et al., (2005)²⁹ and Pisacane et al.,²⁴. The present study says that ID is one of the possible risk factors for febrile seizures. Developmental problems, the risk of paediatric stroke, the occurrence of febrile seizures, and breath holding spells are perhaps the tip of the iceberg, of the neurological consequences of ID. The findings of the present study similar with study done by Voorhess ML et al.³⁰

Limitations of the study

- It was a single center study.
- Limited sample size.
- Other clinical parameters were studied.

CONCLUSION

The present study showed that hemoglobin, MCV, serum ferritin, and serum iron levels are significantly lower in children suffering with febrile seizures, suggesting that a low iron status has an important role in children with febrile seizures. Thus, ID is predictor for febrile convulsion. Consequently, measuring serum ferritin is a specific, sensitive, and a reliable test for detecting iron depletion in the early stages of the disease itself and the best standard for determining the total body iron storage. Therefore, complete blood count and screening for ID with serum iron studies are recommended in the work up of children with the first febrile convulsion itself. A follow-up study

of patients found to be iron deficient at the time of a first febrile seizure to determine the incidence of subsequent febrile seizures after the treatment for ID would be of great interest.

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Authors Contribution:

MN- Concept and design of the study, prepared draft of manuscript, review the literature and manuscript preparation, interpretation of results and analysis;
RHN- Concept, coordination, statistical analysis and data interpretation, preparation of manuscript and revision of the manuscript

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