

## A case–control study to find the association between iron deficiency anemia and simple febrile seizures in children between 6 months and 5 years of age group

Radhika Vaghela<sup>1</sup>, Sanjay Mandot<sup>2</sup>

From <sup>1</sup>Resident, <sup>2</sup>Professor, Department of Pediatrics, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India

Correspondence to: Dr. Sanjay Mandot, A 13, Saheli Nagar, Udaipur - 313 001, Rajasthan, India. E-mail: drmandot@yahoo.com

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### ABSTRACT

**Background:** Simple febrile seizure (FS) is the most common type of childhood seizure. Iron plays an important role in brain metabolism, neurotransmitter function, and myelination. Iron deficiency anemia (IDA) has been found to be associated with an increased incidence of FS. **Objective:** The objective of the study was to study the prevalence of IDA in simple FS patients and febrile patients without seizure. **Materials and Methods:** All admitted febrile children between 6 months and 5 years were enrolled in the study according to the inclusion and exclusion criteria and a detailed clinical examination was done. Blood samples were collected for complete blood count, blood indices, and serum ferritin. **Results:** IDA was present in 28 out of 50 patients in the case group and 18 of 50 patients in the control group ( $p < 0.05$ ). Mean hemoglobin and mean serum ferritin levels were significantly lower in the case group when compared to the control group ( $p < 0.05$ ). **Conclusion:** All the investigations carried out to evaluate the IDA were significantly lower in the case group as compared to the control group. This suggested that iron-deficient children were more prone to get FS.

**Key words:** Case group, Control group, Iron deficiency anemia, Serum ferritin, Simple febrile seizures

A simple febrile seizure (FS) is the most common childhood seizure. FS occurs between 6 months and 5 years of age at temperature 38°C (100.4°F) or higher without central nervous system (CNS) infection or any metabolic imbalance. Simple FS comprises generalized tonic and clonic activity which is associated with fever, lasting not more than 15 min and not recurring within 24 h [1]. In 2–5% of children, it occurs at least once. Febrile convulsions in the majority of the cases begin in the 2<sup>nd</sup> year of life [2].

FS occurs commonly in children suffering from otitis media, roseola, human herpesvirus 6, *Shigella*, or similar infections [3]. Many independent risk factors (genetics, age, gender, fever, type and duration of seizure, family and developmental history, multiple seizures, and perinatal exposure to antiretroviral drugs) have been studied as potential predictors of recurrent FS. Among these, iron deficiency anemia (IDA) has been found to be associated with an increased incidence of FS [4,5].

Iron plays an important role in the metabolism of several neurotransmitters. In the case of IDA, the levels of aldehyde oxidase, monoamine oxidase, and the expression of cytochrome C oxidase, a marker of neuronal metabolic activity, are decreased. In developing countries, iron deficiency is the most prevalent nutritional problem [6,7]; especially, among infants aged 6–24 months [8]. Iron deficiency can affect a developing brain by altering the development of hippocampus neurons, impairment of energy metabolism, and alterations in synaptic neurotransmitter

systems including norepinephrine, dopamine, glutamate, gamma-aminobutyric acid, and serotonin [9].

IDA is common during the 2<sup>nd</sup> and 3<sup>rd</sup> years of life and is associated with developmental and behavioral impairments; hence, it can influence motor and cognitive skills [10]. As iron plays an important role in the function of various enzymes and neurotransmitters in the CNS, low serum levels of ferritin may lower the seizure threshold [11,12]. The present study was conducted to study the prevalence of IDA in simple FS patients and febrile patients without a seizure and to determine the association between iron deficiency and simple FS.

### MATERIALS AND METHODS

This was a prospective study carried out at the department of pediatrics at a tertiary hospital of Rajasthan from November 1, 2017, to October 31, 2019, after obtaining permission from the Institutional Ethical Committee. It was a case–control study which included a total of 100 patients aged 6 months–5 years according to the inclusion and exclusion criteria. A case group included 50 patients admitted for simple FS and the control group consisted of 50 children admitted with febrile illness without seizures.

Sample size of 100 patients was calculated using the formula:  $n = Z\alpha^2 P(1-P) = 1.96 \times 50(1-50) = 49$ ,  $E^2 = 100$ . ( $Z\alpha = 1.96$  at 95% confidence level,  $P = 50\%$  by the unbiased association,  $1-P = 50\%$ ,  $E = 10\%$  by absolute error). Thus, 50 patients each in

the case and control groups were considered for the study. All eligible febrile patients were consecutively enrolled in the study after taking prior informed consent from the parents.

At the time of hospitalization, all subjects underwent a complete systemic examination. The axillary temperature at hospitalization was taken by a digital thermometer and the subjects with the temperature more than 38°C were included in the study. Patients with simple FS (generalized tonic-clonic in nature, lasting for <15 min, no recurrence within 24 h period) were included in the case group. Children with CNS infections such as meningitis, encephalitis, developmental delay, neurodegenerative disorders, seizure due to stroke or metabolic disturbance, CNS hemorrhage, trauma, and vasculitis, atypical FS, anemia due to bleeding, hemolytic anemia, children on iron therapy, and whose parents/guardians did not provide consent for the study were excluded from the study.

The routine hematological investigations such as hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular Hb (MCH), MCH concentration (MCHC), and serum ferritin were evaluated at the time of hospitalization for all cases and controls. For children aged 6 months–2 years, IDA was defined as Hb <10.5 g/dl, MCV <70 fl, MCH <23 pg, MCHC <30 g/dl, and serum ferritin <10 ng/ml [1]. For children aged 2–5 years, IDA was defined as Hb <11.5 g/dl, MCV <75 fl, MCH <24 pg, MCHC <31 g/dl, and serum ferritin <10 ng/ml [1].

The statistical analysis was done using Statistical Package for the Social Sciences Version 20.0 statistical analysis software. Data were expressed in frequency and percentage as well as mean and standard deviation (SD). To elucidate the association and comparisons between different parameters, Chi-square test was used. Student's t-test was used to compare mean values between two groups.  $p < 0.05$  was considered statistically significant. The continuous variables were expressed as mean±SD and categorical variables were expressed in the percentages.

## RESULTS

Out of 100 patients, 50 each belonged to the case and the control group, respectively. In the case group, 28 patients were male and 22 were female with a male predominance (56%) for simple FS. The majority of the patients belonged to the age group between 6 and 12 months. In the case group, 28 patients had fever between 102 and 103°F and upper respiratory tract infection as etiology of fever followed by acute gastroenteritis, exanthem, and urinary tract infection in six subjects.

In the case group, a family history of seizures was recorded in 12 patients and the remaining 38 patients did not have any family history. However, in the control group, 2 had a family history and the remaining 48 did not have any family history of seizures ( $p=0.004$ ). Around 62% of patients had onset of seizures on the 2<sup>nd</sup> day of fever with an average duration between 1 and 5 min. IDA was present in 28 patients in the case group and 18 patients in the control group ( $p=0.0001$ ). As demonstrated in Table 1, Hb, MCV, MCH, MCHC, and mean serum ferritin levels in the case group were significantly lower as compared to that in the control group.

**Table 1: Comparison of various laboratory parameters between the case and control groups**

Investigations	Case group (Mean±SD)	Control group (Mean±SD)	p-value
Mean Hb (g/dl)	9.40±0.926	10.36±0.921	0.0001
Mean MCV (fl)	68.80±10.365	78.80±6.194	0.0004
Mean MCH (pg)	22.82±25.92	25.92±3.568	0.002
Mean MCHC (pg/dl)	31.48±0.953	32.46±1.110	0.0001
Serum ferritin (ng/ml)	14.86±9.81	33.72±17.64	0.0001

SD: Standard deviation, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration

## DISCUSSION

In the present study, the majority of cases of simple FS occurred in 6–12 months of age. This is in accordance with the study by Vaswani *et al.* [11] and Kumari *et al.* [13]. A unique age specificity of maturing brain's sensitivity to fever is reported in a review by Waruiru and Appleton [14]. In the present study, 12 patients in the cases and 2 in the control group had a family history of seizure ( $p=0.004$ ). This is in agreement with the studies by Kumari *et al.* [13] and Rahul [15] which showed strong evidence of positive family history as a risk factor for FS.

In the present study, the majority of the patients had fever between 102 and 103°F. Similar results were obtained in the study by Majumdar [16]. IDA was found in 46% of the total patients, which was higher than those observed by Kumari *et al.* [13]. However, Al Hawsawi *et al.* [17] recorded IDA in 49% of patients which was higher than the present study. In the present study, the incidence of anemia was higher among cases as compared to controls ( $p=0.0001$ ). Similarly, Rahul [15] reported a significant difference between the case and control groups. In our study, Hb in the case group was significantly lower than that of the control group ( $p=0.0001$ ). This was in accordance with the results obtained by Shaikh *et al.* [18].

The mean MCV for the case group was less than that of the control group ( $p=0.0004$ ) which is according to the results obtained by Shaikh *et al.* [18] and Kamalammal and Balaji [19]. The mean MCH was significantly lower in cases than that in the control group ( $p=0.002$ ) which is similar to the studies by Kamalammal and Balaji [19] and Karimi *et al.* [20]. In the present study, the mean MCHC in cases was significantly lower than that in controls ( $p=0.0001$ ) which is similar to the study by Kamalammal and Balaji [19].

The mean serum ferritin in cases was significantly less than that in the controls ( $p=0.0001$ ) which was in accordance with the results obtained by Kumar and Sasikumar [21]. This difference can be explained by the overall higher prevalence of IDA in India. However, Bidabadi and Mashouf [22] and Yousefichaijan *et al.* [23] concluded that the mean value of serum ferritin for the case group was higher than that of the control group. The present study had a few limitations. The study did not include follow-ups of the case group children who were on iron supplements after a simple FS episode.

## CONCLUSION

The results of the present study have shown an association between IDA and simple FS. It opens up new possibilities for the prevention of FS by simple interventions of iron supplementation or dietary alterations.

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