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Association of serum iron and serum calcium levels in children with febrile seizures

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ABSTRACT

Objectives: The current case–control study was conducted to investigate the relationship of iron deficiency anemia and calcium levels with febrile seizures (FSs) in children.

Materials and Methods: The study included 200 children ranging in age from 6 to 60 months. One hundred cases had FSs, including simple FSs and rest; 100 controls had a short history of febrile illness (<3 days) without seizures. A statistical analysis of the data was carried out using Statistical Package for the Social Sciences version 23.

Results: The mean weight, height, and head circumference of cases and controls are 9.73 ± 2.51 kg and 10.63 ± 3.34 kg, 79.66 ± 11.08 cm and 85.43 ± 15.55 cm, and 46.37 ± 2.79 cm and 46.83 ± 3.72 cm, respectively. As per the Indian Academy of Pediatrics, 27% of cases and 37% of controls had protein energy malnutrition (PEM). In cases and controls, the mean hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and red cell distribution width values were 9.23 ± 1.30 and 10.78 ± 1.60 gm/dL, 68.83 ± 8.86 and 78.59 ± 9.82 fl, 25.40 ± 3.47 and 28.50 ± 3.60 pg, and 18.73 ± 1.77 and 16.44 ± 1.76, respectively, and are statistically significant. Patients had lower serum ferritin levels than controls. The mean blood calcium levels in cases and controls were 9.13 ± 0.64 and 9.05 ± 0.93 mg/dL, respectively (P = 0.507). Iron deficiency anemia was found in 26% of cases and 7% of controls (P value <0.001). Hypocalcemia was reported in only 18% of patients and 23% of controls (P = 0.38).

Conclusion: There is a clear correlation between FSs and iron deficiency. The majority of data suggests that hypocalcemia is unlikely to be the cause of FSs. Early detection and intervention of iron deficiency in children could help in the prevention and recurrence of FSs.

Keywords: Anemia, Hypocalcemia, Children, Febrile seizures, Case–control study

INTRODUCTION

Febrile seizures (FSs) occur between the ages of 6 and 60 months, with a temperature of 38°C or higher, and are not the consequence of a central nervous system (CNS) infection or any metabolic imbalance that arises without a history of preceding afebrile convulsions. The stated prevalence rates of FS vary throughout the world, whereas methodological variances may be a factor in these geographical disparities.[1] Genetic, environmental, and sociodemographic variables have all been linked to the occurrence of FS.[2,3] According to reports, one out of every 25 children will encounter at least one FS throughout their childhood.[4]

FS ranks as one of the most common reasons for pediatric ER visits, affecting up to one in every twenty children globally. Although FSs are usually harmless, they cause substantial family anguish and concern.

The World Health Organization estimates that anemia, which is mostly caused by iron deficiency, affects 500 million to two billion people worldwide. Iron is a nutrient that is necessary not only for hemoglobin production but also for various neurochemical events. Neurological symptoms such as low attention span, learning impairments, poor memory, delayed motor development, and behavioral abnormalities are well-documented to occur. As a result, iron deficiency can predispose to neurological problems such as FS. Much research has been conducted to explore the etiology and natural history of FS as well as to assess alternative therapeutic options. Although most research has shown iron deficiency as a risk factor for having FS,[5] some studies believe it is less

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often connected. Because the findings are contradictory, more research into the link between iron-deficient anemia and FS is required.

Hypocalcemia is a frequent metabolic anomaly that can result in convulsions, muscular cramps, tetany, seizures, and paresthesia. Water and electrolyte balance abnormalities are common with any acute febrile condition. It has been proposed that a shift in blood calcium levels may increase the vulnerability to seizures.

Keeping this in mind, case–control research was conducted to assess the relationship, if any, between iron deficiency anemia and hypocalcemia and FSs in children.

MATERIALS AND METHODS

After getting approval from the institute's ethics committee (Letter number: 32/CRC/2018, dated August 27, 2018), this hospital-based prospective case–control research was conducted in the pediatric ward of the Baba Raghav Das (BRD) Hospital in Gorakhpur, Uttar Pradesh, India, from July 2018 to June 2019. Children aged 6–60 months were enrolled in the study after obtaining written informed consent. The research is divided into two groups: (1) cases (n = 100): all cases of FSs between the ages of 6 and 60 months, including simple FSs and (2) controls (n = 100): children hospitalized with febrile illness but no seizures. Children with previous FSs, epilepsy, acute CNS infection, iron therapy, intravenous calcium, or any chronic systemic ailment (cardiac, renal, metabolic, or malignancy) were excluded from the study.

Baseline assessment

Demographic information, seizure information, the cause of the febrile illness, a family history of FS, and examination results on admission were all recorded. Demographic data comprising name, age, gender, and registration number; nutritional assessment included rating PEM according to the Indian Academy of Pediatrics (IAP) classification.[6] Weight was assessed using a digital weighing scale, and length was recorded using an infantometer on children under 12 months. All data are entered into a pre-designed pro forma.

Laboratory evaluation

- Hemoglobin and red cell indices, including red cell distribution width (RDW), mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV), along with serum ferritin and calcium levels, were all measured.
- Iron deficiency anemia is described as having hemoglobin <11 g/dL, MCV <70 fl, MCH <27 pg, and serum ferritin <12 µg/L (in the presence of infection <30).
- Total serum calcium values of 8.5 mg/dL are considered hypocalcemia.

Statistical analysis

The data were statistically examined using Statistical Package for the Social Sciences version 23. The independent t-test was used to analyze quantitative variables, whereas the Chi-square test was used to analyze qualitative data. The statistical significance level was set at $P < 0.05$.

RESULTS

One hundred patients (65 males and 35 females) experienced a FS, whereas the remaining 100 controls (58 males and 42 females) experienced a brief bout of feverish illness without seizures. The current study included 65 males and 35 females as cases and 58 males and 42 females as controls. The male-to-female ratio in cases was 1.85:1, whereas it was 1.38:1 in controls. This implies a gender-equal distribution of children among controls and cases. In terms of age distribution, 21% of cases are 6–11 months old, whereas the control group contains 28% in this age range. The mean weight, height, and head circumference of cases and controls are 9.73 ± 2.51 kg and 10.63 ± 3.34 kg, respectively, 79.66 ± 11.08 cm and 85.43 ± 15.55 cm and 46.37 ± 2.79 cm and 46.83 ± 3.72 cm. 81% of the patients had seizures lasting 5 min or less, indicating that the majority belonged to this category. 91% of instances had a generalized tonic–clonic seizure, and the rest 9%, had a focal seizure. In the current study, 9% of patients had a family history of febrile convulsions, whereas none of the controls did. Upper respiratory tract infection (URTI) was the cause of fever in 63% of cases and 52% of controls, followed by lower respiratory tract infection (LRTI) and age.

According to the IAP, 27% of cases and 37% of controls had PEM. 18% and 9% of cases had Grade 1 and 2 PEM, whereas 21% and 16% of controls had Grade 1 and 2 PEM, respectively.

At the time of admission, the mean temperature of patients and controls was 102.13 ± 0.86°F (38.96 ± 0.48°C) and 101.73 ± 0.56°F (38.73 ± 0.31°C), respectively. A higher temperature was reported in cases compared to controls at admission, with a $P < 0.001$.

Blood parameters

In cases and controls, the mean hemoglobin, MCV, MCH, and RDW values were 9.23 ± 1.30 and 10.78 ± 1.60 gm/dL, 68.83 ± 8.86 and 78.59 ± 9.82 fl, 25.40 ± 3.47 and 28.50 ± 3.60 pg, and 18.73 ± 1.77 and 16.44 ± 1.76. They are statistically significant, with low hemoglobin, MCV, and MCH found more than controls and high RDW seen in cases [Table 1].

Serum ferritin levels in patients and controls were 39.06 ± 16.23 and 79.02 ± 22.37 microgm/L, respectively. The cases have lower serum ferritin levels than controls (P = 0.001) [Table 2].

Table 1: Blood parameter comparison.

Parameter	Cases		Controls		*P*–value
	Mean	Standard deviation	Mean	Standard deviation	
Hemoglobin (g/dL)	9.23	1.30	10.78	1.60	<0.001
MCV (fl)	68.83	8.86	78.59	9.82	<0.001
MCH (pg)	25.40	3.47	28.50	3.60	<0.001
RDW (%)	18.73	1.77	16.44	1.76	<0.001

RDW: Red cell distribution width, MCH: Mean corpuscular hemoglobin, MCV: Mean corpuscular volume

Table 2: Comparison of serum ferritin levels.

	Serum ferritin (microgm/L)	Standard deviation
Cases	39.06	16.23
Controls	79.02	22.37

P<0.001

Table 3: Comparison of serum calcium levels.

	Serum calcium (mg/dL)	Standard deviation
Cases	9.13	0.64
Controls	9.05	0.93

P=0.507

The mean blood calcium levels in cases and controls in the current research are 9.13 ± 0.64 and 9.05 ± 0.93 mg/dL, respectively. The difference is insignificant, with P = 0.507 [Table 3].

Iron deficiency anemia alone was found in 26% of cases and 7% of controls in the current research (P = 0.001). Hypocalcemia was seen in only 18% of patients and 23% of controls (P = 0.381) [Table 4].

Table 4: Iron deficiency anemia and hypocalcemia in case and control groups.

	IDA	Hypocalcemia
Cases	26	18
Controls	7	23
P-value	<0.001	0.381

IDA: Iron deficiency anemia

DISCUSSION

The FS connection to iron deficiency is being researched all around the world. Iron is known to have an important role in brain functioning in addition to its biological impacts. It is essential in the brain for myelin synthesis, neurotransmitter metabolism, and energy metabolism.[7] Iron deficiency was revealed to be a substantial risk factor for FS in children aged 6 months to 5 years old in the current investigation; however, no direct relationship between hypocalcemia and FS was established.

In the current study, the mean age of onset is 21.72 ± 14.28 months. Naveed-ur-Rehman and Billoo (2005) (mean age of cases: 22.97 ± 9.52 months and controls 22.77 ± 11.33 months),[8] and Bidabadi and Mashouf (mean age of cases: 22.86 ± 12.86 and controls 21.91 ± 13.58)[7] are studies that are comparable to the current study. In contrast, studies by Pisacane *et al.*[9] (cases had a mean age of 15 months) and Daoud *et al.*[10] (cases had a mean age of 18.8 months, whereas controls had a mean age of 19.1 months) indicate a younger generation at the onset of febrile convulsions. In the current study, 27% of patients and 37% of controls had graded PEM according to the IAP classification. According to Kumari *et al.*,[11] malnutrition was found in 62% of cases and 52% of controls; nevertheless, the distribution was insignificant (P = 0.238). The current study had 65% males and 35% females, with a male predominance similar to prior studies.[12,13]

Type of seizure

The majority of convulsions in this study were generalized, with 91% of people experiencing simple FS and only around 9% having complex FS. Similar to the current investigation, Salehi Omran *et al.*[14] discovered generalized convulsions in 94.4% of patients and localized convulsions in 5.6% of cases. According to Sadeghzadeh *et al.*,[15] 70% of patients had simple FS, and 30% had complex FS.

Family history of FSs

Many epileptic disorders have a family tendency, and some may be inherited in an autosomal dominant fashion. In the current study, 9% of patients and none of the controls had a family history of febrile convulsions. Kumari *et al.*[11] reported a convulsion family history in 26% of cases and 13% of controls (P = 0.004). Aly *et al.*[16] discovered that 87.5% of patients and 12.5% of controls had a family history of FS, whereas Sultan *et al.*[17] discovered that 71% of cases and 12% of controls did. These two studies show a greater prevalence of FS.

Etiology of fever

As in the current research, URTI is also the most prevalent cause of fever in other investigations.[10,13]

Temperature

Fever is required for the onset of seizures. When the patients were admitted, their mean temperature was 102.13 ± 0.86°F (38.96 ± 0.48°C) (P = 0.001), meaning that the cases had higher temperatures than the controls. Sultan *et al*.[17] discovered that the highest temperature during a convulsion was 1030°F. Vaswani *et al*.[18] found that the mean temperature of patients and controls was 38.6 ± 0.36°C and 38.5 ± 0.29°C, respectively, which was statistically insignificant (P = 0.13).

Comparison of hematological parameters and iron deficiency anemia

Worldwide, research on the relationship between iron deficiency and FS has produced mixed results. The results of this study show that the values of Hb (mean 9.23 ± 1.30 gm/dL; P < 0.001), MCV (mean 68.83 ± 8.86Fl; P < 0.001), MCH (mean 25.40 ± 3.47 pg; P < 0.001), and serum ferritin (mean 39.06 ± 16.23 microgm/L; P < 0.001) were statistically significant and lower in cases than in controls, whereas the value of RDW (mean: 18.73 ± 1.77 %; P < 0.001) was higher in cases than in controls. Kumari *et al*. (2012)[11] stated iron deficiency as Hb 11 gm/dL, serum ferritin 12 nanogram/mL, and RDW >15% and reported that iron deficiency is more prevalent in cases with P = 0.001 and an adjusted odds ratio of 4.5 (95% confidence interval), outcomes that are consistent with the current study's conclusion that iron deficiency and simple febrile convulsions have a statistically significant association. Sherjil *et al*.[19] found that children with iron-deficient anemia are twice as likely as children with febrile illness alone to experience seizures, with an odds ratio of 1.93. Hartfield *et al*.[20] found a similar finding, reporting that children with FSs are twice as likely to develop iron deficiency as children with febrile illness alone. Amirsalari *et al*.[12] reported that 26.5% of cases had low plasma ferritin (12 ng/mL), compared to 29.5% of controls (P = 0.623); only 3.8% of cases had low MCV (70 Fl), compared to 6.8% of controls (P = 0.312); and only 3% of cases had low Hb (10.5 g/dL), compared to 6% of controls (P = 0.241). These findings were not consistent with the findings of the current study, which concluded that there was no causal relationship between iron deficiency anemia and FS.

Comparison of hypocalcemia and FSs

Regular biochemical testing is not required in FS, as reported by Kenney and Taylor.[21] Rarely aberrant results from routine serum sodium, calcium, and glucose assays may be obtained, especially in young children. There is no connection between serum electrolytes and FS, according to the American Academy of Pediatrics.[22] In research conducted by Nickavar *et al*.,[23] 175 children aged 23 months were put into three groups. The first experienced simple FSs, the second experienced repeated FSs, and the third acted as a control. Serum calcium levels were 9.17, 8.97, and 9.32 mg/dL, with no difference between groups and a nominal P-value equivalent to the current study. As a result, the association is vulnerable. As a result, serum electrolyte alterations are unlikely to have a clinically relevant impact on seizures. In research that looked at the function of electrolytes in seizure recurrence, Sayedzadeh and Hemati[24] noticed that the mean calcium levels were 9.23 ± 0.76 mg/dL in patients with simple FS and 9.88 ± 0.8 mg/dL in patients with recurrent FS, with no statistically significant distinction between both groups. In the current study, which included only 18% of cases and 23% of controls, there was little evidence that hypocalcemia was related to FSs (P = 0.381). Hypocalcemia as a cause of FS is improbable, at least according to the majority of studies.

CONCLUSION

FSs and iron deficiency are strongly correlated. The majority of data suggest that hypocalcemia is unlikely to be the root cause of FSs. Children in this age range may experience fewer FSs if iron deficiency is identified early and treated promptly.

Ethical approval

The author(s) declare that they have taken the ethical approval from the institutional ethics committee, wide letter number: 32/CRC/2018, dated August 27, 2018.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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