

Research Article

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

Mohammed R. Naseer*, Kailash Chandra Patra

Department of Pediatrics, ESIPGIMSR and ESIC Model Hospital, Andheri, Mumbai-400093, Maharashtra, India

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*Correspondence:

Dr. Mohammed R. Naseer,

E-mail: bsbsohail@gmail.com

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ABSTRACT

Background: Objective of current study was to determine association between iron deficiency anaemia and hypocalcemia in children with febrile seizures.

Methods: In this case control study 100 cases and 100 controls with and without seizures were taken, respectively. Iron and calcium deficiency determined in both groups and comparison made individually and additively.

Results: Mean hemoglobin of cases and controls was 9.14 gm% and 9.54 gm% respectively. With a P value of 0.003, being statistically significant, low hemoglobin was seen more in cases than controls. Mean value of serum ferritin in cases being 42.11 microgram/dl is statistically significant with a P value of 0.01 i.e., low serum ferritin seen in cases. Whereas mean value of serum calcium was 9.5 mg% which is statistically insignificant. Additively too iron deficiency and calcium deficiency were not associated with febrile seizures.

Conclusions: There is a positive association between iron deficiency anaemia and febrile seizures, hence it should be excluded. Whereas calcium deficiency and both iron and calcium deficiency are not associated with febrile seizures.

Keywords: Iron deficiency anaemia, Hypocalcemia, Serum ferritin, Serum calcium, Febrile seizures

INTRODUCTION

Febrile seizures are the commonest convulsions occurring between 6 months to 5 years of age without any central nervous system infection.¹ Incidence of febrile seizures is 4.8/1000 children/year.² Febrile seizures are not only agonizing to the parents but also to the child and can cause psychological trauma to both. They have been studied thoroughly since last two decades but the pathophysiology is still unknown till date. Several hypotheses have been postulated and many independent risk factors considered as a predisposing factor.

Iron deficiency is considered to be the commonest micronutrient deficiency not only in developing countries but also worldwide occurring more commonly in age groups of 6 to 24 months. World Health Organization

(WHO) estimates that anaemia, largely due to iron deficiency affects 500 million to two billion people worldwide³. It is not only preventable but treatable too. In certain developing countries, up to 50 percent preschool children have anaemia that is principally due to iron deficiency. Iron is a nutritional element required not only for hemoglobin synthesis but also for many neurochemical reactions like myelin formation, brain energy metabolism, some neurotransmitters and enzyme metabolism such as monoaminoxidase.⁴ Neurological symptoms like poor attention span, learning deficits, weak memory, delayed motor development and behavioral disturbances are well known to occur.^{5,6} Thus it is possible that iron deficiency can predispose to neurological disturbance like febrile seizures. Age of peak incidence of febrile seizures overlaps with that of iron deficiency which is between 6 to 24 months.⁷ Many

studies have investigated the etiology and natural history of febrile seizures and evaluated various management strategies. While most studies have shown iron deficiency as the predisposing factor for development of febrile seizures but other studies opine it to be less frequently associated. Since the results are conflicting, there is a need to explore relationship between iron deficiency anaemia and febrile seizures.

A common biochemical abnormality causing seizures is hypocalcemia, which may manifest as muscle cramps, tetany, seizures and paraesthesia.⁸ During any acute febrile disease, disturbances in water and electrolytes occur frequently. It has been suggested that change in serum calcium might enhance the susceptibility to seizures.

Thus, keeping in view the association of febrile seizures with iron deficiency anaemia and hypocalcaemia, a case control study was conducted to assess association between iron deficiency anemia and hypocalcemia, individually and additively.

METHODS

This is a prospective case control study conducted in Pediatric ward of a reference hospital over a period of one and half years. Children between 6 months to 60 months were included in the study. A written informed consent was obtained from the parents. Two groups were included in the study. Cases being children between 6 months to 60 months with first febrile seizure after ruling out central nervous system infection or any other defined cause of seizure. Controls being children aged 6 months to 60 months admitted with febrile illness without seizures during the same period. Demographic details, seizure details, nature of febrile illness, examination findings on admission were noted according to study proforma. Demographic data included name, age, sex; nutritional assessment was done. All information recorded in a pre-designed proforma. Iron deficiency anaemia defined as:^{9,10}

- Hemoglobin <11 gm/dl,
- MCV < 70 femtoliter,
- MCH <27 picogram,
- Serum Ferritin <12 micro gram/dl.

Hypocalcemia defined as total serum calcium levels <8.5 mg/dl.⁸ Collected data tabulated, graphically displayed. Percentages, arithmetic mean and standard deviation calculated and data statistically analyzed using SPSS (Statistical Package for Social Sciences) version 16. Interferential analysis for quantitative variables done using independent T-test whereas analysis for qualitative data was done using Chi square test. Statistical significance was set at $P < 0.05$.

RESULTS

Results of demographic and hematological parameters comparison are tabulated. Mean age of cases and controls were 21.47 ± 14.24 and 31.72 ± 20.99 months respectively. Cases were more common in males (61%) with an insignificant P value. Etiology of the fever most commonly being Upper Respiratory Tract Infection (URTI) with a P value of 0.112, it is statistically insignificant. Lower Respiratory Tract Infection (LRTI) was more common in cases where as acute gastroenteritis (AGE) was more common in controls.

The mean temperature in cases was $38.9 \pm 0.48^\circ\text{C}$ being higher than in controls of $38.7 \pm 0.31^\circ\text{C}$. The mean values of Hb, MCV and MCH were low in cases compared to controls with statistically significant P values as mentioned in tabular column. Mean values of Serum Ferritin in cases and controls were 42.11 ± 30.46 and 54.97 ± 25.26 respectively, with a P value being 0.01, it is statistically significant, i.e., low serum ferritin seen in cases than in controls. Mean value of serum calcium levels in cases and controls is 9.25 ± 0.63 and 9.12 ± 0.54 respectively. With a P value of 0.128, the difference is not statistically significant. About 17 % of cases and 7% of controls had Iron deficiency anemia only, P value being 0.029 it is statistically significant. 10% of cases and 6% of controls had only hypocalcemia, with P value being 0.298 it is statistically insignificant. 2% of cases and 2% of controls had both Iron deficiency anemia and hypocalcemia, with P value being >0.99 it is statistically insignificant.

Table 1: Demographic data for both cases and controls.

Parameter	Cases	Controls	P value
Age (months)	21.7	31.72	
Sex (%)			
Males	61	56	0.473
Females	39	44	
Etiology of fever (%)			
URTI	66	55	0.122
LRTI	25	26	0.871
AGE	9	19	0.01
Temperature ($^\circ\text{C}$)	38.9 ± 0.48	38.7 ± 0.31	0.001

Table 2: Comparison of blood parameters.

Parameter	Cases Mean \pm SD	Controls Mean \pm SD	P value
Hemoglobin	9.14 ± 0.85	9.54 ± 0.98	0.003
MCV	65.99 ± 5.33	84.01 ± 13.74	0.000
MCH	25.39 ± 3.09	37.06 ± 9.68	0.000
RDW	15.12 ± 1.14	14.17 ± 1.13	0.000
Serum ferritin	42.11 ± 30.46	54.97 ± 25.26	0.01
Serum calcium	9.25 ± 0.63	9.12 ± 0.54	0.128

Table 3: Comparison of iron deficiency of anemia and hypocalcemia.

Parameter	IDA	Hypocalcemia	IDA+Hypocalcemia
Cases	17	10	2
Controls	7	6	2
P value	0.029	0.298	>0.99

DISCUSSION

Febrile seizures are a form of acute symptomatic seizures. Being one of the important pediatric health problems in developing and developed countries, they occur most commonly in age group of 6 to 60 months. Their association with iron deficiency is explored all over the world. There is considerable incidence that iron has an important role in neurological functions in addition to its biological effects. It is needed for neurotransmitter metabolism, myelin formation and brain energy metabolism.¹¹ There is a controversy about relationship between iron deficiency anaemia and febrile seizures. During an acute febrile disease, mild disturbance of water and electrolyte balance occur frequently, changes in which might enhance the susceptibility to seizures and its recurrences. Attempts have been made to identify these predisposing factors. In current study iron deficiency was found as a significant risk factor for febrile seizures in children between 6 months to 5 years of age, but no casual association between hypocalcemia and incident febrile seizure is made.

The mean age of onset in present study is 21.74 ± 14.24 months and that of controls is 31.72 ± 20.99 . In present study 62% of cases were males whereas 39% were females with male preponderance. Whether there is a biological basis for the gender-specific differences in febrile seizure susceptibility or whether boys just contract more fever and therefore are at greater risk, is currently not established.

In present study acute gastroenteritis, URTI and LRTI corresponded to 9%, 66% and 25% respectively, whereas in controls the frequency was 19%, 55% and 26% respectively. There being no statistical difference with respect to URTI and LRTI as the cause of fever. URTI, as in present study is also the most common etiology of fever in other studies too. Study by Majumdar et al.¹⁴ had URTI as the commonest cause with no statistical difference with control group. Sultan et al.¹⁸ found respiratory tract infections as the commonest cause (78% in cases).

Fever is a requirement for development of seizures. Studies suggest temperature $>38^{\circ}\text{C}$ and others 38.4°C as the temperature for development of seizure. In our study the mean temperature of cases at the time of admission was $102.1 \pm 0.88^{\circ}\text{F}$ ($38.9 \pm 0.48^{\circ}\text{C}$).

Association between febrile seizures and iron deficiency is explored all over the world, results being conflicting.

Study by Kumari et al.¹⁹ defined iron deficiency as Hb <11 gm/dl, serum ferritin <12 nanogm/dl and RDW $>15\%$ and found that iron deficiency is more common in cases with $P=0.001$ with adjusted odds ratio of 4.5 (95% CI), findings similar to present study concluding that highly significant association was found between iron deficiency and simple febrile convulsions. Pisacane et al.²⁰ in a study, also had anaemia, significantly more common in cases (30%) than hospital controls (14%) with OR 1 (CI-2.6;1.4-4.8) opining that fever can worsen negative effect of anaemia and seizure can occur as a consequence. Studies by Sherjil et al.²¹ and Hartfield²² done to correlate iron deficiency anaemia and febrile seizures, concluded that children with iron deficiency anaemia are twice likely to develop seizures than children with febrile illness alone. Study by Daoud et al.²³ who evaluated iron status in 75 children with febrile seizures, reported the following in cases: Low Hb-10.6 gm%, with $P=0.27$; Low MCV 73.3, with $P=0.36$; Low MCH of 25% with $P=0.26$. All the above values were statistically insignificant, probably due to less sample size. Similar results found in present study but statistically significant. Whereas plasma ferritin, which is the best measure of iron status in the body, was also reported; mean value of which was 29.5 microgm/dl with a P value of 0.0001, significantly higher proportion of cases had low serum ferritin. In present study too low serum ferritin was found with a P value of 0.029. They concluded that, lower plasma ferritin is associated and may play a role in febrile seizures. Naveed-ur-Rehman et al. & Billoo,¹² Vasvani et al.,²⁴ Jun et al.,²⁵ Saeed et al.,²⁶ Fallah et al.¹³ also found low serum ferritin, Hb, MCV (<70 fl) and MCH (<24 Pg) in cases; results being similar to present study and concluding that low body iron plays an important role in brain metabolism, can down regulate halting many substantial functions of brain and could lead to febrile seizures.

Amirsalari et al.,²⁷ with 132 cases found low Hb (<10.5 gm/dl) in only 3% of cases compared to 6% of controls with $P=0.241$, low MCV (<70 Fl) in only 3.8% of cases compared to 6.8% of controls with a $P=0.312$ and low plasma ferritin (12 microgm/dl) in 26.5% of cases compared to 29.5 % of controls with a $P=0.623$; results of which being dissimilar to present study, concluded that no casual relationship was found between iron deficiency anaemia and febrile seizures. In a study by Korbinsky et al.²⁸ also estimated iron status and found that low Hb (<110 gm/dl), low MCH (<20 pg) and low MCV (<65 Fl), more in controls but with insignificant P values and opined that iron deficiency may protect against development of febrile seizures. Bidabadi & Mashouf¹¹ too found iron deficiency anemia less frequently in cases than in controls but with no protective effect of development of anemia (OR=1.75).¹¹ While Talibain et al.²⁹ did a study and found low Hb, Low MCV and low MCH in controls than in cases concluded that there is no association between serum ferritin and febrile seizures.

Kenny & Taylor have shown that routine biochemical tests are not necessary in febrile seizures.³⁰ Routine measurements of serum sodium, calcium and glucose may result in very low number of abnormal findings, particularly in children. American Academy of Pediatrics reported no significant casual association between serum electrolytes and febrile seizures.³¹ Study done by Nickavar et al.,³² where 175 children were enrolled with a mean age group of 23 months were divided into three groups. 1st with simple febrile seizures, 2nd with recurrent febrile seizures and the 3rd, as control. Serum calcium levels were 9.17, 8.97 and 9.32 respectively, with no difference of serum calcium levels in all three groups with an insignificant P value similar to present study. Hence, the weakness of association. Alteration in serum electrolytes is thus unlikely to play a clinically significant role in causing seizures. Sakha & Barzgar, in a similar study, where ionized calcium was estimated found no meaningful difference with a P value of 0.460.³³ Sayedzadeh & Hemati, in a study, where the role of electrolytes in recurrence of convulsion was assessed, mean calcium levels being 9.23 ± 0.76 in patients with simple febrile seizures and 9.88 ± 0.8 in recurrent febrile seizures, where no significant difference was found between the two.³⁴ Study by Chiarelli et al.,³⁵ where 159 children with febrile seizures were taken and compared with a group of healthy subjects and children with fever. Serum calcium levels were low in febrile convulsions unlike in the present study. In present study only 10% of cases and 6% of controls had hypocalcemia, with a P value of 0.298, association of hypocalcemia with febrile seizures is insignificant. Like majority of studies, hypocalcemia as a cause of febrile seizure is unlikely.

Akbayrams et al.³⁶ in a study, where 48 children with febrile seizures were compared with age matched controls found low serum calcium ($P < 0.05$) and iron ($P = 0.001$), where it was aimed to find if any change in element levels occur in children with febrile seizures. In present study only 4% of cases had both iron deficiency anemia and febrile convulsions. In literature there are inadequate studies relating serum calcium & iron deficiency anemia, both additively, in children with febrile seizures. Hence, conclusion of that sum of iron deficiency anaemia and hypocalcemia causing febrile seizures cannot be made.

Table 4: Comparison of age of onset of febrile seizures.

Study	Mean age of cases (months)
Naveed-ur-Rehman & Billoo ¹²	22.97 ± 9.52
Fallah et al. ¹³	23 ± 14.3
Bidabadi et al. ¹¹	22.86 ± 12.86
Majumdar et al. ¹⁴	24
Yousefchaijan et al. ¹⁵	20 to 33
Waheed & Butt ¹⁶	20 to 33
Sadeghzadeh et al. ¹⁷	12 to 23
Present study	21.74 ± 14.24

CONCLUSION

The findings suggest that a considerable percentage of children having febrile seizures suffer from iron deficiency, hence iron deficiency anaemia can serve as reinforcing factors for febrile seizures and needs to be excluded. Whereas calcium deficiency and additively iron and calcium deficiency is not associated with febrile seizures.

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