

## Study of Serum Iron, Calcium and Zinc Status in Correlation to Febrile Seizure in Children Admitted to a Tertiary Care Hospital in Bihar

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### Abstract

**Aim:** To evaluate the correlation of serum iron, serum calcium and serum zinc levels in children with febrile seizures.

**Methods:** This prospective case control study was conducted on 120 Children between 6 months to 5 years who were admitted to a tertiary care hospital in Bihar over a period of one and half year from April 2020 to October 2021 fulfilling the inclusion criteria. The case group consisted of 60 patients with febrile seizures and the control group included 60 febrile children without seizures. Demographic details, seizure details, nature of febrile illness, examination findings on admission and investigations were noted according to study protocol.

**Results:** Mean age of cases and controls was  $21.12 \pm 15.26$  and  $36.9 \pm 21.19$  months respectively. Among cases 61.67 % were males. The mean temperature in cases was  $102.12 \pm 0.83^\circ\text{F}$  being higher than that of controls ( $98.87 \pm 0.278^\circ\text{F}$ ;  $P = 0.0012$ ). The mean values of Hb, MCV and MCH were low in cases compared to controls with statistically significant P values. Mean value of Serum Ferritin in cases and controls was  $40.14 \pm 29.65 \mu\text{g/l}$  and  $58.16 \pm 25.08 \mu\text{g/l}$  respectively ( $P = 0.0014$ ) i.e., low serum ferritin was seen in cases than in controls. No significant difference in mean value of serum calcium was noted among cases and controls. Mean value of serum zinc level in cases was  $49.84 \pm 38.62 \mu\text{g/dL}$  which was lower than controls ( $92.17 \pm 33.5 \mu\text{g/dl}$ ;  $P = 0.0001$ ).

**Conclusion:** The children having febrile illness suffer from iron deficiency and zinc deficiency can serve as reinforcing factors for febrile seizures and needs to be excluded whereas calcium deficiency is not associated with febrile seizures.

**Keywords:** Febrile seizure, Serum zinc, Serum ferritin, Serum calcium, Iron deficiency

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## Introduction

Febrile seizure is one of the most common causes of hospitalization of children in pediatric ward in INDIA. The international league against epilepsy (2014) defines febrile seizure (FC) as “a seizure associated with a febrile illness (rectal temperature more than 38° C) in the absence of a CNS infection, metabolic abnormality, any acute electrolyte imbalance and not meeting criteria for other acute symptomatic seizures or who don't have prior afebrile seizures [1,2]. Febrile seizures are most common between 6 months and 5 years of age, with a peak incidence at about 18 months of age. An onset above 7 year is rare, although it does occur. Febrile convulsions tend to occur in families, although the exact mode of inheritance is not known and varies between families. Febrile convulsion susceptibility trait is inherited by autosomal dominant pattern with reduced penetrance [2]. The risk of another child having febrile convulsions is one in five with one affected sibling and one in three if both parents and a previous child had febrile convulsions. The seizure incidence in offspring of individuals with a history of febrile convulsion was 10%. [2] The pathogenesis of this condition is still unknown. However, several theories, such as genetic basis, reduction of serum as well as cerebrospinal fluid (CSF) zinc and magnesium level and low Gamma- amino butyric acid (GABA) have been proposed. [3,4,5] Low CSF GABA values have been reported in association with several seizure disorders, including febrile convulsion [6,7]. Zinc is known to play a control role in the immune system, and zinc- deficient persons experience increased susceptibility to a variety of pathogens. Zinc also functions as an antioxidant and can stabilize membranes[6]. Zinc modulates the affinity of neurotransmitters such as glutamate to their receptors and facilitates the inhibitory effect of calcium on Nmethyl- D-aspartate receptors and thus

prevents the excitatory neuronal discharge [6,7,8].

A common biochemical abnormality causing seizures is hypocalcemia, which may manifest as muscle cramps, tetany, seizures and paraesthesia. It has been suggested that change in serum calcium might enhance the susceptibility to seizure. Iron is a nutritional element required not only for haemoglobin synthesis but also for many neurochemical reactions like myelin formation, brain energy metabolism and neurotransmitter synthesis etc [2]. Neurological symptoms like poor attention span, learning deficits, weak memory, delayed motor development and behavioural disturbances are well known to occur due to anaemia [13]. Thus, it is possible that iron deficiency can predispose to neurological disturbance like febrile seizures. Age of peak incidence of febrile seizure overlaps with that of iron deficiency, which is between 6 to 24 months.

## Material and methods

This prospective case control study was carried out in the Department of Pediatrics, Darbhanga Medical College, and Hospital, Laheriasarai, Darbhanga, Bihar, India, after taking the approval of the protocol review committee and institutional ethics committee.

Total 120 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. Hemoglobin, Red cell indices viz., MCV, MCH, RDW; Serum Ferritin and Serum Calcium levels was estimated (XT-2000i haematology analyse). All information recorded in a pre-designed proforma. The parents of all patients were provided a written informed consent for inclusion in to the study, which was approved by the Institutional Ethics Committee. Iron deficiency anaemia is defined as: <sup>[2,3]</sup> Hemoglobin <11 gm/dl, MCV < 70 femtoliter, MCH <27 picogram, and Serum Ferritin <12 micro gram/dl. Hypocalcemia is defined as total serum calcium levels <8.5 mg/dl.<sup>6</sup> Collected data was 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

Mean age of cases and controls were  $21.12 \pm 15.26$  and  $36.9 \pm 21.19$  months respectively. Cases were more common in

males (61.67%) with an insignificant P value. Etiology of the fever most commonly being Upper Respiratory Tract Infection (URTI) with a P value of 0.163, it is statistically insignificant. Lower Respiratory Tract Infection (LRTI) was more common in cases whereas acute gastroenteritis (AGE) was more common in controls.

The mean temperature in cases was  $102.12 \pm 0.83^\circ\text{F}$  being higher than in controls of  $98.87 \pm 0.278^\circ\text{F}$  ( $P = 0.0012$ ). 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  $40.14 \pm 29.65 \mu\text{g/L}$  and  $58.16 \pm 25.08 \mu\text{g/L}$  respectively, with a P value being 0.0014, it is statistically significant, i.e., low serum ferritin seen in cases than in controls. Mean serum Iron in cases and controls was  $51.37 \pm 37 \mu\text{g/dL}$  and  $82.25 \pm 18.61 \mu\text{g/dL}$  respectively ( $P = 0.0001$ ) and mean serum zinc in cases and controls was  $49.84 \pm 38.62 \mu\text{g/dL}$  and  $92.17 \pm 33.5 \mu\text{g/dL}$  respectively ( $P = 0.0001$ ). Serum Iron and zinc level was significantly low in cases. Mean value of serum calcium levels in cases and controls is  $9.26 \pm 0.58$  and  $9.29 \pm 0.32$  respectively. With a P value of 0.749, the difference is not statistically significant.

**Table 1: Demographic data for both cases and controls**

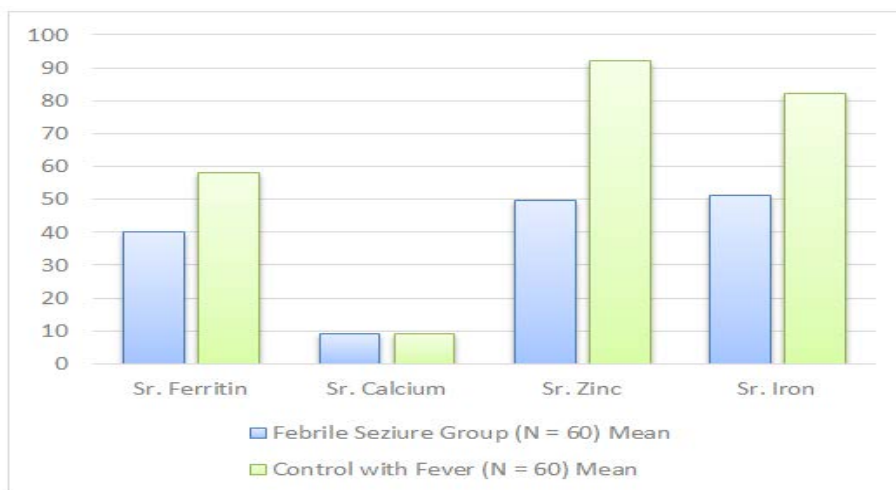
Parameter	Cases	Controls	P value
Age (months)	$21.12 \pm 15.26$	$36.9 \pm 21.9$	
<b>Sex (%)</b>			
Males	37(61.67)	35(58.33)	0.455
Females	23(38.33)	25(41.67)	
<b>Etiology of fever (%)</b>			
URTI	40(66.67)	32(53.33)	0.163
LRTI	15(25)	16(26.67)	0.758
AGE	5(8.33)	12(20)	0.01
Temperature ( $^\circ\text{F}$ )	$102.12 \pm 0.83^\circ$	$98.87 \pm 0.278^\circ$	0.0012

**Table 2: Comparison of blood parameters**

Parameter	Cases	Controls	P value
	Mean ± SD	Mean ± SD	
Haemoglobin (mg/dl)	9.08 ± 0.74	9.63 ± 1.01	0.0025
MCV (fl)	65.6 ± 6.29	84.76 ± 13.35	0.0001
MCH (pg)	25.29 ± 3.08	37.78 ± 9.5	0.0001
RDW	15.15 ± 1.08	14.14 ± 1.33	0.0001
Serum ferritin (µg/L)	43.01 ± 31.02	55.36 ± 24.77	0.0014
Serum iron (µg/dL)	51.37 ± 37	82.25 ± 18.61	0.0001
Serum calcium (mg/dL)	9.26 ± 0.58	9.29 ± 0.32	0.749
Serum zinc (µg/dL)	49.84 ± 38.62	92.17 ± 33.5	0.0001



**Figure 1: Comparison of Blood parameters in cases and controls**



**Figure 2: Mean serum Iron, ferritin, calcium and zinc level of cases and controls**

**Discussion**

Febrile seizure is one of the most frequently occurring seizure disorders

among children between the ages of six months and five years in India. Being one of the important paediatric health

problems in developing and developed countries, its association with various probable risk factors has been explored by various studies.

In our study about 61.67 % of the study population were males among the cases and the mean age for the febrile seizure was  $21.12 \pm 15.26$  months. This was similar to other studies done previously. Among the illness associated with febrile seizures, upper respiratory tract infection was the most common associated condition, as documented in the previous studies. Similar finding was reported from our study with 66.67% of cases found to have upper respiratory tract infection as an associated illness.

**Serum iron, ferritin level and blood indices.** In our study, values of Hb (Mean  $9.08 \pm 0.74$  gm/dl; P 0.0025), MCV (Mean  $65.6 \pm 6.29$  fl; P 0.0001), MCH (Mean  $25.29 \pm 3.08$  pg; P 0.0001) and Serum Ferritin (Mean  $40.14 \pm 29.65$  microgm/L; P 0.0014) were lower in cases compared to controls whereas value of RDW (Mean  $15.15 \pm 1.08$  %; P 0.0001) was higher in cases and were statistically significant. Mean serum Iron in cases was  $51.37 \pm 37$  µg/dL and in febrile illness group was  $82.25 \pm 18.61$  µg/dL respectively. Serum Iron level was significantly low in cases (P = 0.0001). This was similar to a study done by Abbaskhanian *et al* [10], Pisacane *et al* [11], Rehman *et al* [12] and others although some studies [13,15,16,18], found no correlation between anemia and febrile seizure [14]. Association between febrile seizures and iron deficiency is being explored all over the world but results are conflicting. Study by Kumari *et al* [13] defined iron deficiency as Hb <11 gm/dl, serum ferritin <12 ng/dl and RDW >15% and found that iron deficiency is more common in cases with P=0.001 with adjusted odds ratio of 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* [11] 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* [15] and Hartfield *et al* [16] 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* [17] 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. Naveed-ur-Rehman *et al.* & Billoo, [18] Vasvani *et al.*, [19] and others [20,21,22,23] 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.

**Serum Calcium:** In the present Mean value of serum calcium levels was  $9.26 \pm 0.58$  mg/dl in cases and  $9.29 \pm 0.32$  mg/dl in controls. No significant difference in serum calcium was observed in cases and controls (P = 0.749). Similarly, results are obtained from Seyedzadeh *et al's* research [23] and also in the study of Rutter *et al* [24] and others. In contrast to the present study, Zargarian *et al* [25] and others showed that serum levels of calcium, were significantly lower in the case group.

**Serum zinc levels:** Zinc modulates GABA action and facilitate the NMDA receptor activity thereby causing termination of

excitatory neuronal impulses from the brain<sup>6</sup>. A low zinc level thus can precipitate seizure by inducing abnormal epileptic electrical discharges [7,8]. In our study, Mean serum zinc in cases was  $49.84 \pm 38.62 \mu\text{g/dL}$  and in febrile illness group was  $92.17 \pm 33.5 \mu\text{g/dL}$  respectively. Serum zinc level was significantly low in cases. ( $P = 0.0001$ ). A study done by Ganesh et al showed that mean Zinc levels in cases and controls were  $32.17 \pm 15.05$  and  $87.6 \pm 17.6 \mu\text{g/dl}$  respectively. According to Mahyar *et al* [26], mean zinc in cases and controls were  $62.84 \pm 18.40$  and  $85.70 \pm 16.76 \mu\text{g/dl}$  respectively. Waqar Rabbani *et al* [27] found that low zinc levels may be a risk factor for development of febrile convulsions. According to a study done by Hassan et al [28], median Zinc levels in cases and controls were  $53 \mu\text{g/dl}$  and  $93 \mu\text{g/dl}$  respectively. Our study shows a positive correlation of zinc deficiency and febrile seizure among children. [29]

### Conclusion

In conclusion, lower levels of serum iron and serum zinc were associated significantly with febrile seizures. No positive correlation could be established to signify low serum calcium levels as a risk factor of febrile seizures. However, more extensive controlled studies with larger sample sizes are recommended.

### Reference

- Operational Classification of Seizure Types by the ILAE (2017) Position paper of the ILAE Commission for Classification and Terminology
- Kliegman, Robert. Nelson Textbook of Pediatrics. Edition 21. Philadelphia, PA: Elsevier, 2020.
- Karimi, Parviz, et al. "Association of Iron Deficiency Anemia and Febrile Seizure in Asia: A Systematic Review and Meta-Analysis." Iranian Journal of Neonatology 9.1 (2018).
- Shajari H, Shajari A, Azizkhan H, Barzegari R. Correlation of Serum Ferritin and Calcium Level with Febrile Seizures: A Hospital-Based Prospective Case-Control Study. *Maedica (Bucur)*. 2021;16(3):420-425.
- Sharif MR, Kheirkhah D, Madani M, Kashani HH. The Relationship Between Iron Deficiency and Febrile Convulsion: A Case-Control Study. *Glob J Health Sci*. 2015 Jun 25;8(2):185-9.
- Srinivasa, S., and M.N. Manjunath. "Serum zinc levels in children with febrile seizures." *Journal of Evolution of Medical and Dental Sciences*, vol. 3, no. 12, 24 Mar. 2014, pp. 2983+. Gale Academic OneFile, Accessed 15 Apr. 2022.
- Dr P. Lakshmi Kumari, Dr Sasmita Devi Agrawal. Low Zinc and Iron Status: A Possible Risk Factor for Febrile Seizure. *Journal of Medical Science And clinical Research*, Volume 07 Issue 02 February 2019
- Dr. Sowjan M. (2019). A prospective study of serum zinc levels in children presenting with simple febrile seizures. *Pediatric Review: International Journal of Pediatric Research*, 6(3), 118-121.
- Gardner JW, Dinsmore RC. Evolution of the concept of the febrile seizure as it developed in the American medical literature, 1800-1980. *J Hist Med Allied Sci* 1995 Jul;50(3):340-63
- Abbaskhanian A, VahidShahi K, Parvinnezhad N. The association between iron deficiency and the first episode of febrile seizure. *JBUMS*. 2009; 11:32
- Pisacane A, Sansone R, Impagliazzo N, et al. Iron deficiency anaemia and febrile convulsions: case-control study in children under 2 years. *BMJ*. 1996; 313:343-344.
- Rahman, M. Mizanur, Mirza Md Ziaul Islam, and M. Atiqul Islam. "Clinical Profile of Patients with Febrile Convulsion: A Retrospective Study in a Tertiary Care Pediatric

- Hospital." *Pediatric Education and Research* 5 (2017): 61-64.
13. Kumari PL, Nair MK, Nair SM, Kailas L, Geetha S. Iron deficiency as a risk factor for simple febrile seizures-A case control study. *Indian Pediatr* 2012 Jan;49(1):17-9
  14. Haratipor H, Sohrabi MB, Zolfaghari P, et al. The comparison of serum iron, ferritin and TIBC in children aged 9 months to 6 years with febrile seizure. *Knowledge and Health* 2014; 9:55-60
  15. Sherjil A, us Saeed Z, Shehzad S, Amjad R. Iron deficiency anaemia-A risk factor for febrile seizures in children. *J Ayub Med Coll Abbottabad* 2010 Jul-sep;22(3):71-3
  16. Hartfield DS, Tan J, Yager JY, RosychukRJ, Spundy D, Haines C, Craig WR. Association between iron deficiency and febrile seizures in childhood. *Clin Pediatr(Phila)*:2009 May;48(4):420-(6)
  17. Daoud AS, Batiha A, Abu-Ekteish F, et al. Iron status: a possible risk factor for the first febrile seizure. *Epilepsia* 2002; 43:740-743
  18. Naveed-ur-Rehman, Billoo AG. Association between iron deficiency anaemia and febrile seizures. *J Coll Physicians Surg Pak* 2005 Jun;16(6):338-40
  19. Vaswani RK, Dharask PG, Kulkarni S, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. *Indian Pediatr* 2010 May ;47(5):437-9
  20. Jun YS, Bang HI, Yu ST, Shin SR, Choi DY. Relation between iron deficiency anaemia and febrile convulsions in infants. *Korean J Pediatr* 2010 Mar;53(3):392-396
  21. Yadav D, Chandra J. Iron deficiency beyond anaemia. *Indian J Pediatr* 2011Jan;78(1):65-72
  22. Namakin K, Zardast M, Sharifzadeh G, et al. Serum Trace Elements in Febrile Seizure: A Case-Control Study. *Iran J Child Neurol [Internet]* 2016; 10:57-60. Available from: <https://pubmed.ncbi.nlm.nih.gov/27375757>
  23. Sayedzadeh SA, Hemati M. Serums Sodium & Calcium Level in Children with Simple and Recurrent Febrile Convulsion. *J Kermanshah Univ Med Sci* 2007;10: e81821
  24. Rutter N, Smales OR. Calcium, magnesium, and glucose levels in blood and CSF of children with febrile convulsions. *Arch Dis Child* 1976; 51:141-143.
  25. Bidar S, Zargarian T. Relationship between serum levels of sodium, potassium, calcium, magnesium, zinc febrile seizure. *Journal of Birjand University of Medical Sciences* 2018;40(10)
  26. Mahyar, A. & Varasteh-Nejad, A. Serum zinc level in children with febrile seizure. *Acta Medica Iranica*. 2008:46.
  27. Waqar Rabbani M, Ali I, Zahid Latif H, Basit A, Rabbani MA. Serum Zinc Level in Children Presenting with Febrile Seizures. *Pak J Med Sci*. 2013 Jul;29(4):1008-11.
  28. Khajeh, Ali & Miri-Aliabad, Ghasem & Fayyazi, Afshin. (2015). Serum Zinc Level in Children with Febrile Convulsion. *Zahedan J Res Med Sci (ZJRMS)* 2015; in press.
  29. MANSOUR, M. B., & Ahmedana, S. E. (2020). Assessment of Post Exposure Prophylaxis (PEP) in Omdurman Voluntary Counselling and Testing Center (OVCTC). *Journal of Medical Research and Health Sciences*, 3(1), 836–849.