

## Role of iron deficiency anemia in febrile seizures observed in a tertiary care hospital

Dr. Mirza Md Ziaul Islam<sup>1\*</sup>, Dr. Md Jafar Iqbq<sup>2</sup>

<sup>1</sup> Head, Professor, Department of Pediatric Infectious Diseases and Community Pediatrics, Shishu Hospital and Institute, Dhaka, Bangladesh

<sup>2</sup> Department of Pediatric Infectious Diseases and Community Pediatrics, Shishu Hospital and Institute, Dhaka, Bangladesh

### Abstract

**Background:** Febrile seizure is a common cause of seizure in young children. There is high prevalence of iron deficiency anemia and febrile seizure in preschool children. The objective of this study was to investigate the role of iron deficiency anemia in simple febrile seizure patients.

**Methods:** This prospective case-control study was performed in 50 children with simple febrile seizures as cases and 50 febrile children without seizures as control who were admitted to Bangladesh Shishu (Children) Hospital and Institute. All children were aged between 6 months-5years. The groups were matched in age, gender, height and weight. Laboratory investigations performed were Complete Blood Count including Hemoglobin (Hb), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC), Serum Ferritin.

**Results:** There were lower values of Hematological indices like Mean Hemoglobin, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin Concentration and Serum Ferritin in the cases group compared to the control group but no statistically significant difference was found.

**Conclusion:** This study did not establish any association between iron deficiency anemia and febrile seizures.

**Keywords:** Febrile seizure, iron deficiency anemia, serum ferritin

### Introduction

Febrile seizure is defined as a seizure occurring with febrile illnesses without acute systemic metabolic abnormality that may produce convulsions or nervous system infection in a neurologically normal 6 months to 5years old child [1, 2, 3, 4]. The incidence of febrile seizure is about 2-5% in a healthy child. The exact cause of febrile convulsion is unknown, but genetic and environmental factors may have influence on its occurrence. Factors responsible for the febrile seizures include abnormality in cerebrospinal fluid (CSF) neurotransmitters, CSF neopterin concentration and family history of febrile seizure [7, 8, 9]. Age for peak incidence of febrile seizure is 14 to 18 months, which overlaps with that of iron deficiency anemia which is more pronounced from 6 to 24 months of age [10].

Iron is an essential element for metabolism, with many enzymes depending on iron for its function. Iron deficiency anemia is the most common nutritional deficiency in the children. It is an important micronutrient which is used by almost all the cells in human body. It is also an important co-factor for the several enzymes for their proper functions. Iron also has roles in production of neurotransmitters, DNA duplication and several hormonal functions [11].

Iron deficiency leads to improper myelination and synthesis of tyrosine and tryptophan hydroxylase which are necessary for synthesis and release of neurotransmitters like serotonin, dopamine and gamma amino butyric acid (GABA) [7, 12]. Serum ferritin level is also affected by fever severity, inflammation and by male gender [13]. Iron is a nutritional micro element not only needed for the synthesis of hemoglobin, but also essential for enzymes involved in neurochemical reactions [14, 15] such as myelin formation, brain energy metabolism. Some neuro-transmitters and enzymes metabolism such as monoamine oxidase (MAO) and aldehyde oxidase, are reduced in iron deficiency anemia [10, 18, 19]. Neurological symptoms like poor attention span,

learning deficits, weak memory, delayed motor development and behavioral disturbance caused by iron deficiency are well-known [10]. Despite these facts, some studies show that antipyretics do not affect prevention of seizures caused by fever [20, 21], so other variables that affect this process have special circumstances and considering that fever can intensify the anemia symptoms by increasing body metabolism [19] there is a need to explore relation between febrile seizures and iron deficiency anemia. Many studies have investigated the etiology and natural history of febrile seizures and evaluated various management strategies, but very little information is available about iron deficiency as a risk factor. Previous studies examining the relationship between iron deficiency anemia and febrile convulsions have been conflicting [19, 22, 23, 24]. Some of them concluded that iron deprivation plays a role in the pathogenesis of febrile seizures [19, 23, 25, 26].

In contrast, there are some studies that reported that iron deficiency raises the threshold for seizures [22]. Also, recently some reports have shown that although iron deficiency anemia is less frequent among the cases with febrile seizures, but there is no protective effect of iron deficiency against febrile convulsion [27]. Keeping in mind the prevalence of these two clinical entities, we conducted a case-control study to evaluate the role of iron deficiency anemia in febrile seizures.

### Material and Methods

This was an observational case-control study conducted at Bangladesh Shishu (Children) Hospital and Institute, Dhaka. The study group consisted of 100 children of age 6 months to 5 years admitted during August 2019 to July 2020. Fifty consecutive children admitted with febrile convulsions were the considered as cases, and 50 children treated for febrile illness (gastrointestinal or respiratory cause) without convulsion or previous history of convulsion were taken as

controls. Controls were matched to the cases by gender and age, weight, height, head circumference and the history of using any supplemental iron. Exclusion criteria for all subjects included co-morbid conditions like epilepsy, patients already on iron therapy, patients with delayed development and patients known for other causes of anemia. Children with history of perinatal asphyxia and born with low birth weight babies were also excluded from study. Demographic informations collected for cases and controls included age, sex, height, weight, and head circumference. In all patients who did not have a history of any iron

supplement therapies for previous 30 days were included in the study. Hematological investigations performed were hemoglobin (Hb), (MCH), Mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and plasma ferritin (PF). Anemia was defined as the Hb concentration less than 2 standard deviation (SD), below the mean for that age and sex as per WHO guidelines (Table 1). After data collection, statistical analysis was performed by SPSS-26 and independent t-test used to compare the groups. P value of <0.05 was considered as significant.

**Table 1:** Normal range and criteria taken for defining anemia [28]

Age (6months-5 Years)	Normal Range	Criteria taken for Anemia
Hb (Hemoglobin g/dl )	11-13.6	<11
MCV(Mean corpuscular volume fl)	75-87	<75
MCH(Mean corpuscular hemoglobin pg )	25.4-29.6	<25.4
MCHC (mean corpuscular hemoglobin concentration -g/dl)	32.9-35.7	<32.9
S. Ferritin ( ng /mL)	10-300	<10

**Results**

We studied 100 children with fever, out which 50 children were having simple febrile convulsion and comprises of cases while 50 children with fever of respiratory or gastrointestinal cause without convulsion or history of convulsions were studied as controls. In our study, out of 50 children from cases, 35 were boys and 15 were girls. Among the controls, 39 were male and 11 were female children. Mean age for the case group was 18.16 ± 8.09 months while among the control group mean age was 20.64 ± 5.16 months. There was no significant difference in

height, weight and head circumference among the both groups. (Table-2). Among the cases, 54% children were anemic and among the control group, 27% were anemic according to the criteria taken for anemia in the study .There was no statistical significant difference in routine blood examination finding including CBC, serum electrolytes, LFT and RFT value of both groups of iron deficiency anemia among two groups in comparison to hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and serum ferritin (Table-3).

**Table 2:** Demographic profile

	Cases	Control	t value/p
Age(Mean ± SD) in Months	18.16 ± 8.09	20.64 ± 5.16	t=1.80/p=NS*
Sex(Male: Female)	35:15	39:11	t=0.83/p=NS
Height (Mean ± SD) in cm	80.29 ± 7.45	85.27 ± 5.68	t=3.47/p=NS
Weight(Mean ± SD)	11.08 ± 1.43	11.80 ± 1.20	t=0.137/p=NS
Head Circumference (Mean ± SD) in cm	46.79 ± 1.91	46.73 ± 4.50	t=0.07/p=NS

\*NS=Not Significant

There was no significant difference noted between two groups in demographic characteristics, clinical presentation except for convulsions and routine blood and electrolytes

examination. Hematological profile of both groups is described in table 3 and not showing any significant difference

**Table 3:** Hematological Profile

	Cases	Control	t value/ p value
Hemoglobin (gm/dl)	10.86 ±1.23	12.72 ±1.33	t=0.97/p=NS
MCV(fl) (Mean ± SD)	72.37±5.77	74.07±5.34	t=1.52/p=NS
MCH (pg) (Mean ± SD)	23.02±2.88	23.72±3.85	t=1.03/p=NS
MCHC(gm/dl) (Mean ± SD)	31.76 ±1.79	32.09 ±1.94	t=0.89/p=NS
Ferritin(ng/ml) (Mean ± SD)	42.17 ±17.15	50.40 ±30.12	t=1.66/p=NS

**Discussion**

Febrile seizures are most common convulsions of early childhood and incidence reported varies from 2-5% to 14% at different part of world [5]. Several studies were conducted to address association between iron deficiency anemia and febrile seizures, but fail to provide unequivocal results. In this study, basic demographic characteristics, anthropometry value and routine investigations values were comparable in two groups with no significant difference. In our study, the result shows that the Mean Hemoglobin, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Mean Corpuscular

Hemoglobin Concentration and Serum Ferritin were comparatively less in case group compared with control group, but the difference was not statistically significant. Pisacane<sup>19</sup> reported a significantly higher rate of iron-deficiency anemia among children with first febrile seizure than in their controls. In the study of Naveed-ur- Rehman<sup>[23]</sup>, serum ferritin level was significantly lower in cases as compared to controls and suggested that iron deficient children are more prone to febrile seizures. Hartfield DS. *et al* <sup>[25]</sup>, reported that children with febrile seizures were almost twice as likely to be iron deficient as those with

febrile illness per se and suggested that screening for iron deficiency should be considered in children presenting with febrile seizure. Daoud AS *et al* <sup>[26]</sup> found serum ferritin level was significantly lower in children with first febrile seizure than in the reference group, suggesting a possible role for iron insufficiency in first febrile seizure. Vaswani *et al* <sup>[29]</sup>, had concluded that iron deficiency could be a potential risk factor for febrile seizure in children, and in study of Jun Y S <sup>[30]</sup>, results were that the iron deficiency anemia is associated with febrile convulsion, and screening for iron deficiency anemia should be considered in children with febrile convulsions. In contrast, Bidabadi *et al* <sup>[27]</sup> found that mean iron level and serum ferritin were higher in the convulsive group with no statistically significant differences, and Kobrinsky *et al* <sup>[22]</sup> suggested that anemia raises the threshold for first febrile and in study of Im S *et al* <sup>[31]</sup>, shown that iron deficiency may thereby raise the febrile seizure threshold like previous studies. Febrile convulsion is a multi-factorial disease. Independent risk factors for febrile convulsions are height of temperature, family history of febrile convulsions, fever episodes per year, history of maternal smoking or alcoholism during pregnancy. It is also found that children with iron deficiency anemia are mostly from low socio-economic status and may have deficiency of other micronutrients like zinc, magnesium, selenium and copper which may act as important confounding factors <sup>[32]</sup>. The problem with cases- control study was that the subjects we include were from hospital admission which is influenced by so many factors like availability of health services, severity of diseases, social class and certain unidentified variables and not the true representative of the population.

### Conclusion

On the basis of this study, we can arrive to conclusion that although lower mean values of hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin and serum ferritin were found in cases group compared with control group but no statistically significant difference were observed in both group. One of the limitations of our study was the small sample size. Finally, a community based case control study or Meta-analysis should be carried out to find out the association between febrile seizure and iron deficiency anemia

### References

1. Daoud A. Febrile convulsion: review and update. *J Pediatr Neurol*,2004;2:9–14.
2. Sadinejad M, Mohsenzadeh A. Determining serum level of magnesium in children with febrile seizures. *J Nutr Sci Vitaminol*,2005;7:105–8.
3. Al-Ajlouni SF, Kodah IH. Febrile convulsions in children. *Neurosciences*,2000;5(3):151–5.
4. Leung AK, Robson WL. Febrile seizures. *J Pediatr Health Care*,2007;21(4):250–5.
5. Mikati MA, Kliegman RM, Behrman RE, Stanton BF. Seizures in childhood. In: Nelson Textbook of Pediatrics. 19th ed. Philadelphia: WB Saunders, 2011, 2013–8.
6. Vestergaard M, Basso O, Henriksen TB, Ostergaard J, Olsen J. Febrile convulsions and sudden infant death syndrome. *Arch Dis Child*,2002;86(2):125–6.
7. Knight M, Ebert J, Parish RA, Berry H, Fogelson MH. Gamma-aminobutyric acid in CSF of children with febrile seizures. *Arch Neurol*,1985;42(5):474–5.
8. Kawakami Y, Fukunaga Y, Kuwabara K, Fujita T, et al. Clinical and immunological significance of neopterin measurement in cerebrospinal fluid in patients with febrile convulsions. *Brain Dev*,1999;21(7):458–60.
9. Berg AT, Shinnar S, Shapiro ED, Salomon ME, Crain EF, Hauser WA. Risk factors for a first febrile seizure: A matched case-control study. *Epilepsia*,1995;36(4):334–41.
10. Sherjil A, Saeed Z, Shehzad S, Amjad R. Iron deficiency anaemia: a risk factor for febrile seizures in children. *J Ayub Med Coll Abbottabad*,2010;22(3):71–3.
11. Hartfield D. Iron deficiency is a public health problem in Canadian infants and children. *Paediatr Child Health*,2010;15(6):347–50.
12. Heydarian F, Vatankhah H. The role of anemia in first simple febrile seizure in children aged 6 months to 5 years old. *Neurosciences*,2012;17(3):226–9.
13. Kumari PL, Nair MK, Nair SM, Kailas L. Iron deficiency as a risk factor for simple febrile seizures: a case control study. *Indian Pediatr*,2012;49(1):17–9.
14. Beard JL, Erikson KM, Jones BC. Neurobehavioral analysis of developmental iron deficiency in rats. *Behav Brain Res*,2002;134(1-2):517–24.
15. Rouault TA, Cooperman S. Brain iron metabolism. *Semin Pediatr Neurol*,2006;13(3):142–8.
16. Badaracco ME, Siri MV, Pasquini JM. Oligodendrogenesis: the role of iron. *Biofactors*,2010;36(2):98–102.
17. Erikson KM, Jones BC, Hess EJ. Iron deficiency decreases dopamine D1 and D2 receptors in rat brain. *Pharmacol Biochem Behav*,2001;69(3-4):409–18.
18. Chen Q, Beard JL, Jones BC. Abnormal rat brain monoamine metabolism in iron deficiency anemia. *J Nutr Biochem*,1995;6(9):486–93.
19. Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A, et al. Iron deficiency anaemia and febrile convulsions: case-control study in children under 2 years. *BMJ*,1996;313(7053):343.
20. Uhari M, Rantala H, Vainionpää L, Kurttila R. Effect of acetaminophen and of low dose intermittent diazepam on prevention of recurrences of febrile seizure. *J Pediatr*,1995;126(6):991–5.
21. Van Stuijvenberg M, Derksen-Lubsen G, Steyerberg EW. Randomized controlled trial of ibuprofen syrup administered during febrile illnesses to prevent febrile seizure recurrences. *Pediatrics*,1998;102(5):e51.
22. Kobrinsky NL, Yager JY, Cheang MS, Yatscoff RW. Does iron deficiency raise the seizure threshold? *J Child Neurol*,1995;10(2):105–9.
23. Naveed-ur-Rehman, Billoo AG. Association between iron deficiency anemia and febrile seizures. *J Coll Physicians Surg Pak*,2005;15(6):338–40.
24. Millichap JG. Iron insufficiency as a risk factor for febrile seizures. *AAP Grand Rounds*,2002;8(6):62–3.
25. Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C. The association between iron deficiency and febrile seizure in childhood. *Clin Pediatr (Phila)*,2009;48(4):420–6.

26. Daoud AS, Batieha A, Abu-Ekteish F. Iron status: a possible risk factor for the first febrile seizure. *Epilepsia*,2002;43(7):740–3.
27. Bidabadi E, Mashouf M. Association between iron deficiency anemia and first febrile convulsion: a case-control study. *Seizure*,2009;18(5):347–51.
28. Taylor MRH, Holland CV, Spencer R, Jackson JF. Hematological reference range for school children. *Clin Lab Haematol*,1997;19(1):1–5.
29. Jun YS, Bang HI, Yu ST. Relationship between iron deficiency anemia and febrile convulsion in infants. *Korean J Pediatr*,2010;53(3):392–6.
30. Vaswani RK, Dharaskar PG, Kulkarni S. Iron deficiency as a risk factor for first febrile seizure. *Indian Pediatr*,2010;47(5):437–9.
31. Im S, Ah JK, Choi BJ, Lee IG, Whang KT. The relationship between iron deficiency anemia and febrile seizure. *J Korean Child Neurol Soc*,2003;11(1):55–60.
32. Huang CC, Wang ST, Chang YC, Huang MC, Chi YC, Tsai JJ. Risk factors for a first febrile convulsion in children: a population study in southern Taiwan. *Epilepsia*,1999;40(6):719–25.