

Simple Febrile Seizure and Iron deficiency Anaemia-Is there any association?.

1st author- Dr. Alok Raina, MD Pediatrics, SMGSH, GMC Jammu

2nd and corresponding author- Dr.Preeti Sharma, SMGSH, GMC Jammu

Background Febrile seizures occurs mostly in children 14–18 months of age, which overlaps with the maximum prevalence age of iron-deficiency anemia, which is between 1 and 2 years of age. It is well established that iron deficiency may cause some behavioral and developmental problems. The relationship between iron deficiency and febrile seizure is not yet well determined, the present study was conducted to see the association between iron deficiency anaemia and simple febrile seizures. **Methods** -This prospective case control study was conducted in SMGS Hospital, GMC Jammu from January 2018 to December 2020 after taking approval from institutional ethical committee. Cases included children of age group 6 months to 5 years presenting with simple febrile seizure to the casualty or OPD of this hospital. For each case, a control was selected with similar age group and same sex who came for short duration fever (less than 3 days) but without seizures. deficiency was defined as per WHO criteria After proper consent of parents of the study children, blood samples of the study children were sent for the above mentioned investigations in hospital's central laboratory. Samples were taken during afebrile period. **Results**- Total 200 subjects were included in the study, 100 in each group. Iron deficiency anaemia was seen in 46 subjects(46%) in case group and in 13(13%) subjects in control group. The results were statistically significant { $p < 0.0001$, odds ratio(95% CI) 5.70(2.82 TO 11.51)}. **Conclusion**-Iron deficiency anaemia can be considered as a risk factor for febrile seizures and treatment of iron deficiency anaemia may prevent occurrence of febrile seizures.

Key Words-Simple febrile seizure, iron deficiency anaemia, complete blood count, serum ferritin

Febrile Seizures are the most common cause of convulsions in children and a frequent cause of emergency hospital admissions. Between 2% and 5% of children (more common in boys) in Europe and the United States experience at least one febrile seizure before the age of 5 years [1-3]. Although earlier Indian studies suggested that up to 10% of children experience a febrile seizure, recent data indicate that the incidence rate in India is similar to western figures [4,5]. Febrile seizures occurs mostly in children 14–18 months of age, which overlaps with the maximum prevalence age of iron-deficiency anemia, which is between 1 and 2 years of age [6]. Iron deficiency is the most common trace element deficiency that leads to a decrease in the production of hemoglobin, causing IDA. Iron is also essential for the metabolism of the brain and neurotransmitters and in the production of myelin, which is crucial for nerve cell function and can lower the amplitude and threshold of neuron excitation [7]. It is also well understood that iron is a cofactor that is necessary in several enzymes and plays an important role in neurotransmitter production and function, hormonal function, and DNA duplication. In this way, iron deficiency can affect the function of the nervous system and thereafter increases the risk of convulsions [8]. Iron is an essential element for the metabolism of the body and the proper function of many enzymes depends on its presence at an adequate level. Iron is involved in the metabolism of neurotransmitters and enzymes such as monoaminoxidase, cytochrome, peroxidase, and catalase. Also, it is well established that iron deficiency may cause some behavioral and developmental problems [9]. However, the studies carried out so far have reported conflicting results. Some studies have reported that in the patients with iron deficiency, febrile convulsion is significantly higher than that in the control group [6,10-12]. On the contrary, some authors have concluded that the risk of febrile seizure in anemic children seems to be less than that in children with no febrile seizure [13] and that iron deficiency can be a protective mechanism against convulsions by increasing the convulsion threshold [14]. Other studies have shown that iron deficiency plays no role in pediatric febrile seizures [15,16]. Since the relationship between iron deficiency and febrile seizure is not yet determined, chance or other unknown factors can be considered as causes [17]. Considering the above results, the present study was conducted to see the association between iron deficiency anaemia and simple febrile seizures.

Methods- This prospective case control study was conducted in SMGS Hospital, GMC Jammu from January 2018 to December 2020 after taking approval from institutional ethical committee. Cases included children of age group 6 months to 5 years presenting with simple febrile seizure to the casualty or OPD of this hospital. Diagnostic criteria for simple febrile seizures, based on AAP Clinical Practice Guidelines[18], included seizure associated with fever (≥ 100.4 deg F) and seizure was generalized, short duration (less than 15 minutes), no recurrence of seizures within 24 hours, child is otherwise neurologically healthy and without any neurological abnormality before and after the episode of seizure, with age group between 6 months to 5 years. For each case, a control was selected with similar age group and same sex who came for short duration fever (less than 3 days) but without seizures. Children with signs of CNS infections, electrolyte imbalance, neurodevelopmental delay, hepatosplenomegaly, those with chronic liver, renal, cardiac, gastrointestinal, endocrinal or any other chronic disorder disorders were excluded from the study. Iron deficiency was defined as per WHO criteria[19]: hemoglobin less than 11g/dl, mean corpuscular volume(MCV) less than 72fl, mean corpuscular hemoglobin(MCH) less than 24pg, mean corpuscular hemoglobin concentration(MCHC) less than 30g/dl, total iron binding capacity(TIBC) less than 210 μ g/dl, transferrin saturation less than 15%, red cell distribution width(RDW) more than 15% and serum ferritin less than 30 μ g/l. After proper consent of parents of the study children, blood samples of the study children were sent for the above mentioned investigations in hospital's central laboratory. Samples were taken during afebrile period.

Results- Total 200 subjects were included in the study, 100 in each group. In each group there were 58(58%) males and 42(42%) females. Mean age of cases was 3.5 ± 1.3 years and that of controls was 3.2 ± 1.1 years. Comparison of hematological parameters between cases and controls is statistically significant[table1]. Iron deficiency anaemia was seen in 46 subjects(46%) in case group and in 13 subjects in control group(13%)[table2]. The results were statistically significant { $p < 0.0001$, odds ratio(95% CI) 5.70(2.82 TO 11.51)}.

Table1 :-Comparison of hematological parameters between cases and controls.

| Parameters | Cases(n=100) | Controls(n=100) | P value |
|----------------------------|----------------|-----------------|----------------------|
| Hb | 10.02 \pm 1 | 11.5 \pm 1.5 | <0.0001 [†] |
| MCV | 70 \pm 7.5 | 85 \pm 5.1 | <0.0001 [†] |
| MCH | 19 \pm 2.1 | 28 \pm 2.6 | <0.0001 [†] |
| MCHC | 26 \pm 4.2 | 33 \pm 3.3 | <0.0001 [†] |
| RDW | 17 \pm 1.2 | 13.2 \pm 2.1 | <0.0001 [†] |
| TIBC | 340 \pm 34 | 230 \pm 20 | <0.0001 [†] |
| Transferrin saturation (%) | 12.1 \pm 1.1 | 16 \pm 1.2 | <0.0001 [†] |
| Serum ferritin | 36 \pm 10 | 44 \pm 12 | <0.0001 [†] |

[†] Independent t test

Table 2:-Comparison of iron deficiency anemia between cases and controls.

| Iron deficiency anemia | Present | Absent | Total | P value | Odds ratio(95% CI) |
|------------------------|------------|-------------|--------------|----------|---------------------|
| Cases(n=100) | 46(46.00%) | 54(54%) | 100(100.00%) | <0.0001* | 5.70(2.82 to 11.51) |
| Controls(n=100) | 13(13%) | 87(87%) | 100(100.00%) | | |
| Total | 59(29.50%) | 141(70.50%) | 200(100.00%) | | |

* Chi square test

Discussion- In the present study, maximum cases of febrile seizures were reported in males as compared to females. In study conducted by Pathan HG in 2017, preponderance of males was observed over females among cases of febrile seizures[21]. Mean age of cases was 3.5 ± 1.3 years and that of controls was 3.2 ± 1.1 years. Kumari et al., Pisacane et al., Vaswani et al., and found similar result in their study[7,22,23].

Prevalence of anaemia is approximately four times higher in children who had simple febrile seizures than in children without febrile seizure in our study. Our study also revealed that iron deficiency anaemia has a significant association with simple febrile seizures. Thus, iron deficiency anaemia can be considered a significant risk factor for the occurrence of febrile seizures. Kumari et al in their study showed 63.6% of children with simple febrile seizure had iron deficiency anaemia with crude odds ratio of 5.34(3.27-8.73)[7]. Pisacane et al. found similar results with odds ratio of 3.3(1.7-6.5)[22]. Study conducted by Jehangir et al. also showed similar results with odds ratio of 5.17[24]. Sherjil et al. in their study have shown that 31.85% of subjects who presented with febrile seizures had iron deficiency anaemia with odds ratio of 1.93[25]. All hematological parameters in present study were significantly abnormal in those who presented with seizures that those who didn't. Similar results were seen in study conducted by Sharma et al. who revealed that mean serum ferritin levels, values of hemoglobin and MCV were significantly low in children who had simple febrile seizures vs those who had not[26]. Similar results were shown by Jehangir et al and Sherjil et al.[24,25].

Conclusion- There is association between iron deficiency anaemia and simple febrile seizures. Thus iron deficiency anaemia can be considered as a risk factor for febrile seizures and treatment of iron deficiency anaemia may prevent occurrence of febrile seizures. Also patients with simple febrile seizures should be screened for iron deficiency anaemia to prevent its recurrence.

- Hackett R, Hackett L, Bhakta P. Febrile seizures in a South Indian district: Incidence and associations. *Dev Med Child Neurol* 2007; 39(6): 380-4.
- Gourie-Devi M, Gururaj G, Satishchandra P, et al. Prevalence of neurological disorders in Bangalore, India: A community-based study with a comparison between urban and rural areas. *Neuroepidemiology* 2004; 23(6): 261-8.
- Berg AT. Are febrile seizures provoked by a rapid rise in temperature? *Am J Dis Child* 2013; 147(10): 1101-3.
- Rantala H, Uhari M, Hietala J. Factors triggering the first febrile seizure. *Acta Paediatr* 2005; 84(4): 407-10.
- Berg AT, Shinnar S, Shapiro ED, et al. Risk factors for a first febrile seizure: A matched case-control study. *Epilepsia* 1995; 36(4): 334-41.
- Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C et al. The association between iron deficiency and febrile seizures in childhood. *Clin pediatr* 2009; 48:420-426.
- 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; 49:17-19.
- Heydarian F, Vatankhah H. The role of anemia in first simple febrile seizure in children aged 6 months to 5 years old. *Neurosciences (Riyadh)* 2012; 17:226-229.
- Nasehi MM, Abbaskhanian A, Omran MRS. Association between iron deficiency anemia and febrile seizure: a systematic review and meta-analysis. *J Pediatr Rev* 2013; 1:13-18.
- Ur-Rehman N, Billoo A. G. Association between Iron Deficiency Anemia and Febrile Seizures. *J Coll Physicians Surg Pak.* 2005;15(6):338-40.
- Daoud A. S, Batieha A, Abu-Ekteish F, Gharaibeh N, Ajlouni S, Hijazi S. Iron Status: A Possible Risk Factor for the First Febrile Seizure. *Epilepsia.* 2002;43(7):740-743.
- Momen A, Nikfar R, Karimi B. Evaluation of Iron Status in 9-month to 5-year-old Children with Febrile Seizures: A Case-control Study in the South West of Iran.
- Talebian A, Momtazmanesh N. Febrile Seizures and Anemia. *Iran J Child Neurology.*
- Kobrinsky N. L, Yager J. Y, Cheang M. S, Yatscoff R. W. Tenenbein M. Does Iron Deficiency Raise the Seizure Threshold? *J Child Neurol.* 1995;10(2):105-9.
- Salehi Omran M. R, Tamaddoni A, Nasehi M. M, Babazadeh H, Alizadeh Navaei R. Iron Status in Febrile Seizure: A Case-control Study. *Iran J Child Neurology.* 2009:40-43.
- Amirsalari S, Keihanidost Z, Ahmadi M, Sabouri A, Kavemanesh Z, Afebrile seizureshar P. Relationship between Iron Deficiency Anemia and Febrile Seizures. *Iran J Child Neurology.* 2010;14(1):27-30.
- Bidabadi E, Mashouf M. Association between Iron Deficiency Anemia and First Febrile Convulsion: A Case-control Study. *Seizure.* 2009;18:347-351.
- American Academy of Pediatrics. Febrile seizures. *Pediatr.* 2008;121:1281-6
- World Health Organization. Iron deficiency anaemia. Geneva: Assessment, Prevention and Control. A Guide for Program Managers. WHO/NHD/013; 2001

20. Pathan HG, Bari AN, Kokiwar PR. A study of etiology and characteristics of febrile convulsions and epilepsy among children. *Int J Contemp Pediatr*. 2017;4(6):2093-7.
21. 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; 313:343.
22. Vaswani RK, Dharaskar PG, Kulkarni S, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. *Indian Pediatr* 2009; 47:437–439.
23. Bhat JA, Sheikh SA, Bhat SU, Ara R. Association of iron deficiency anemia with simple febrile seizures: a hospital-based observational case–control study. *Menoufia Med J* 2020;33:882-5
24. 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; 22:71–73.
25. Sharma AK, Sharma R. Evaluating the association between iron deficiency and simple febrile seizure in children aged 6 months to 5 years: a case control study. *Int J ContempPediatr* 2018; 5:1003–1007.