

IRON DEFICIENCY ANEMIA - A RISK FACTOR FOR FEBRILE SEIZURES IN CHILDREN

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ABSTRACT

Objective: To find out the association between iron deficiency anemia and febrile seizures in children.

Study Design: Analytical: case-control study.

Place and Duration of Study: The study was conducted at Paediatrics department, Pak Emirates Military Hospital Rawalpindi, from May 2013 till Oct 2013.

Material and Methods: Two Hundred patients were selected through non probability consecutive sampling, one hundred in each group i.e. patients with febrile seizures and patients without febrile seizures. The blood sample of cases and controls were taken at the time of admission and was sent for assessment of hemoglobin (Hb), serum ferritin level, mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular volume (MCV). The samples were analyzed for iron deficiency anemia and compared in both groups (patients with febrile seizures and those without febrile seizures).

Results: In the febrile seizures group 58 (58%) were anemic with a hemoglobin level less than 10gm/dL and 59 (59%) had a low plasma ferritin of less than 10ng/dL. In the control group 39 (39%) were anemic with a hemoglobin level less than 10gm/dL and 26 (26%) had a plasma ferritin of less than 10ng/dL. The frequency of anemia with low MCV, MCHC and serum ferritin was more in the febrile seizure group 38% as compared to 20% in controls (*p*-value = 0.002).

Conclusion: The children with febrile seizures have lower hemoglobin, MCV, MCHC and serum ferritin level as compared to the control groups suggesting that iron deficiency anemia has a positive role in the pathogenesis of febrile seizures.

Keywords: Anemia, Febrile Seizures, Ferritin, Iron deficiency anemia.

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INTRODUCTION

Anaemia, one of the most common disorders, affecting the children of the developing world, is mostly caused by iron deficiency. It has been estimated by World Health Organization that anaemia, mainly caused by iron deficiency, affects about 500 million and two billion people worldwide^{1,2}. Anaemia, which is mainly caused by iron deficiency, is affecting about 50% of pre-school children of the developing countries¹. Iron deficiency anaemia is the most common dietary and haematological disease of infancy and early childhood^{3,4}. Iron is a

very important component of haemoglobin, which transports oxygen in the body. Iron also plays an important role in various neuro-chemical enzymatic reactions⁵. Iron deficiency anaemia causes various neurological symptoms like behavioural disturbances, delayed motor development, poor attention span, learning difficulties and weak memory and is a well-known fact⁵. Thus, there is a possibility that iron deficiency anaemia may act as a predisposing risk factor towards other neurological disturbances like febrile seizures⁶. Febrile convulsions also called as febrile seizures, are the most common convulsive disorder affecting 2-5% of children⁷⁻⁹. Febrile convulsions occur in children between ages of 6 months to 5 years of age having a core temperature of 38°C or higher without any source of CNS infection or acute brain insult^{10,11}. The peak age of

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incidence of febrile seizures is 14-18 months¹²⁻¹⁴ while the peak age of incidence of iron deficiency anaemia is 6-24 months. There is a considerable overlap in the peak incidence age of febrile seizures and iron deficiency anaemia. This point toward a need, to explore the association, between iron deficiency anaemia and febrile seizures¹⁵.

The association between iron deficiency anaemia and febrile seizures has not been researched much despite the facts mentioned above. Khalid *et al* found in their study that 31.2% children with febrile seizures have iron deficiency anaemia as compared to 11.6% in controls¹⁶. Sherjil *et al* conducted a local study and found out that 31.85% of cases (50 out of 157) had iron deficiency anaemia whereas, 19.6% of controls (30 out of 153) were found to have iron deficiency¹ with odds ratio of 1.93 while Hartfield *et al*¹⁷ conducted an international research to find out that 9% of cases had iron deficiency (ID) and 6% had iron deficiency anemia (IDA), compared to 5% and 4% of controls respectively and concluded that children of febrile seizures are twice as likely to be iron deficient as compared to controls¹⁸. Kobrinsky *et al* deducted the protective effect of iron on febrile seizures while Piscane *et al* believed that there is higher incidence of febrile seizures in patients of iron deficiency anemia as compared to controls⁷. Bidabadi *et al* mentioned that iron deficiency anemia was less frequent among the cases with febrile convulsion, as compared to the controls but the difference was not statistically significant. It was deducted that there is no protective effect of iron deficiency against development of febrile convulsion (odd ratio=1.175)¹⁹. The results of these studies are conflicting. Considering the prevalence of iron deficiency anaemia and febrile seizures and the difference of opinion about the association between these two clinical entities, a case control study was conducted to find out the association between iron deficiency anaemia and febrile seizures. So, treating the iron deficiency anaemia appropriately may decrease the incidence of febrile seizures.

MATERIAL AND METHODS

The analytical case control study was conducted at the Paediatrics department, Pak Emirates Military Hospital, Rawalpindi, a tertiary care hospital. The duration of study was six months from 1 May 2013 to 31 Oct 2013. The sample size was calculated using world health organization (WHO) calculator, level of significance was 5% and power of the test was 80% and anticipated population proportion 1 0.312 and anticipated population proportion was 0.116¹⁶. The total sample was 200 children, 100 in each group. The samples were selected through non probability consecutive sampling. In case group

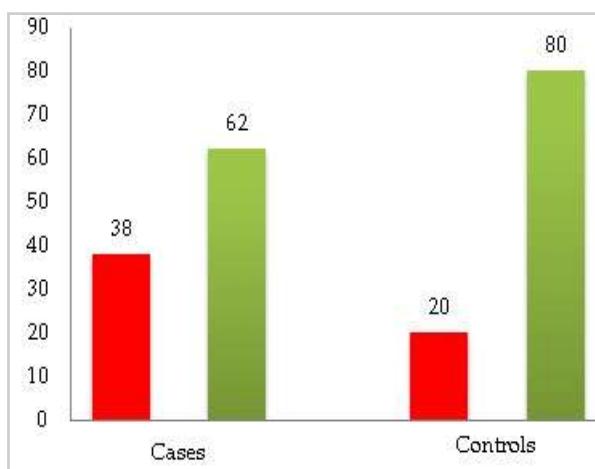


Figure: Bar diagram showing Iron deficiency anemia in cases and controls $p\text{-value}=0.002$.

children having age between 6 months to 6 years were selected. The children in case group were of either gender and having minor febrile illness like acute respiratory illness like flu, pharyngitis, tonsillitis and acute otitis media. Whereas the children with any detectable CNS infection like meningitis, which was ruled out clinically by the signs like neck rigidity and bulging fontenella and the children with previous history of afebrile seizures were excluded. Controls were taken of age 6 months to 6 years who came to child OPD for routine healthy baby checkup or vaccination with minor febrile illness in the absence of febrile seizures were included in control group while the children with previous history of afebrile seizures and developmental delay or CNS conditions like

cerebral palsy were excluded from the study. The study was commenced after informed consent from parents of children participating in the study. The blood samples of both case and control group were taken at the time of admission or examination in OPD. The samples were analyzed by the pathology laboratory of military hospital. The hemoglobin, MCHC, MCV and serum ferritin were measured. The samples were analyzed by Sysmax KX-21 hematology counter and Access II Immunoassay Analyzer (Beckman Coulter). There was no intervention done in the

accessed by using the Chi Square test and *p*-value of 0.05 was taken as significant.

RESULTS

During the study period 100 patients who had febrile seizures admitted to the hospital and 100 controls were enrolled in study. The age of both group ranged from 6 months to 6 years of age. In the febrile seizures group the mean age was 30.73 ± 20.69 months and 71 (71%) children were below the age of 36 months while the mean age in the control group was 29.47 ± 20.99 months and there were 71 (71%) children below the age

Table-I: Comparison of Mean of Age, Hemoglobin, MCV, MCHC and ferritin between the febrile seizure (case) and control groups.

S. No.	Groups	Mean	Std. Deviation	<i>p</i> -value
Age (Months)	Cases	30.73	20.69	1
	Control	20.69	20.68	1
Hemoglobin g/dl	Cases	9.36	1.29	0.007
	Control	10.54	1.31	0.007
MCV fL	Cases	67.19	6.39	0.268
	Controls	71.65	9.62	0.268
MCHC g/dl	Cases	29.33	2.73	0.144
	Controls	30.13	3.00	0.144
Ferritin ng/L	Cases	8.60	4.75	0.000
	Controls	20.83	15.10	0.000

TableII: Risk Estimate for iron deficiency anemia and febrile seizures.

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Cases/Controls)	2.452	1.299	4.626
For Cohort IDA = Yes	1.900	1.193	3.025
For Cohor IDA = No	0.775		
N of Valid Cases	200	0.646	0.930

study in the form of treating the patients. The data was entered in predesigned structured proforma. The data was analyzed by statistical software version SPSS 10. Mean and standard deviation (SD) was calculated for quantitative variables like age, hemoglobin, MCHC, MCV and ferritin levels. The data was expressed by using tables and bar diagrams (table-I, II & figure). The febrile seizure group was compared to the control group with regard to hemoglobin, MCHC, MCV and serum ferritin levels. The statistical significance of the difference was

of 36 months. The groups were matched with respect to their age *p*-value was 1. There were 74 (74%) males and 26 (26%) females in the febrile seizures group while there were 73 (73%) males and 27 (27%) females in the control group and *p*-value was 0.83. In the febrile seizures group the mean hemoglobin was 9.36 ± 1.29 gm/dL, the mean, mean corpuscular volume was 67.19 ± 6.39 fL, mean MCHC was 29.37 ± 2.73 and mean ferritin levels were 8.60 ± 4.75 ng/dL. In the control group the mean hemoglobin was 10.54 ± 1.31 gm/dL, the mean, mean corpuscular volume

was 71.65 ± 9.62 , mean MCHC was 30.13 ± 3.00 and mean ferritin levels were 20.83 ± 15.10 ng/dL. There was a significant difference statistically between the febrile seizures group and the control group in the hematological parameters. The *p*-value was 0.005. In the febrile seizures group 58 (58%) children were anemic with a hemoglobin level less than 10gm/dL, 31 (31%) had a low MCV of less than 65 fL, 30 (30%) had a low MCHC and 59 (59%) had a low plasma ferritin of less than 10ng/dL. In the control group 39 (39%) children were anemic with a hemoglobin level less than 10gm/dL, 24 (24%) had a low MCV of less than 65fL, 21 (21%) had a low MCHC and 26 (26%) had a low plasma ferritin of less than 10ng/dL. The frequency of anemia with low MCV, MCHC and serum ferritin was more in the febrile seizure group about 38% as compared to control group 20% and the difference was significant statistically. The *p*-value was 0.002. In order to establish the relationship between anemia and seizures the Odds ratio was calculated. The children with iron deficiency anemia were having a 1.9 times more risk of febrile seizures as compared to the control group with normal hemoglobin with *p*-value= 0.006. So it indicated that there is a difference in the incidence of febrile seizures between the children who are anemic and who have normal hemoglobin concentration.

DISCUSSION

The most common convulsive disorder in the children is febrile convulsions which occur in about 2-5% of children²⁰. As febrile convulsions are associated with the epilepsy later on in the life, the studies have attempted to find out the associations and the risk factors like family history of febrile or afebrile convulsions, perinatal factors and the rate of rise of temperature and temperature peak. It was reported by Pisacane *et al*²¹ that anemia was more prevalent in children with febrile seizures of age less than 2 years. In contrast to this, there was a finding in a study conducted by Kobrinsky *et al*²⁰ that iron deficiency elevates the threshold for the febrile seizures. The metabolism of several neurotrans-

mitters and monoamine oxidases and aldehyde oxidases require iron and the deficiency of iron results in the decrease amount of these neurotransmitters. As iron deficiency anemia is more common in the 2nd and 3rd year of life, this deficiency has a role in the neuro-developmental and behavioral disturbances²². So the role of iron in the pathogenesis of febrile seizures is ambiguous and the results of various studies are conflicting and no specific association was found out by these studies. Kobrinsky²⁰ found out that the serum ferritin levels were lower in the children having febrile seizures as compared to control group. MCV, MCHC and HB was also lower in cases that is children with febrile seizures but the difference was not of statistical significance. Our study showed that the febrile seizures were associated with decreased ferritin level and the difference was significant statistically with the *p*-value=0.000. Pisacane *et al*²¹ also studied the subject in children less than 3 years from Naples and found out the levels of Hb, MCV and serum iron. He found out that 30% children, who suffered from febrile seizures had anemia as compared to 14% of the controls. In this study serum ferritin was not taken into account. Iron plays a very important part in various neurochemical enzymatic reactions²², so its deficiency manifested by low serum ferritin may be the predisposing factor towards the febrile seizures and may lower the threshold for seizures²³. The negative effects of low serum ferritin were enhanced by the febrile episodes and this may be the reason of triggering factor for the seizures. Iron is stored in the body in the form of ferritin. The sensitive, specific and reliable method of ascertaining the iron deficiency at an early age is by measuring serum ferritin level. Serum ferritin is the best predictor of body iron status. Febrile illness may result in the non specific increase of serum ferritin as it is an acute phase reactant. But this confounding factor was taken into account as both the groups were having fever. So the different levels of serum ferritin cannot be attributed to the febrile illness in these groups. The children coming to the hospital belong to almost same

socio economic status as they belong to the soldier and junior commissioned officers of Pakistan. Cases and controls were selected consecutively so that there was no selection bias. Why there is a difference between the level of serum ferritin among the cases and controls is not known. The exact role of the iron in the pathogenesis of febrile seizures is wanting and needs more studies to find a possible role of iron as a protective or predisposing factor towards febrile seizures. There is very limited data on the subject locally. A case control study was conducted in Aga Khan University hospital pediatrics department, Karachi, to find out the possible association between the iron deficiency anemia and febrile seizures. It was found out by the study that iron deficiency anemia was more frequent among the children with febrile seizures as compared to controls as evident by hemoglobin concentration of <10g/dl; *p*-value ≤0.000 and hematocrit <30%; *p*-value ≤0.01, MCV of <70fL; *p*-value ≤0.002, MCH of <24pg, *p*-value ≤0.001 and serum ferritin of <10ng/ml; *p*-value ≤0.000. The children who are deficient in iron are more prone to the febrile seizures as the plasma ferritin level was significantly lower in them as compared to the controls. The prospective follow up study of the children who were iron deficient at the time of their first febrile seizures for the recurrence of febrile seizure will be yielding important results. This study was conducted on small scale but it can be the thrusting force for a larger studies on national level, which will establish the confirm relationship of iron and febrile seizures. But to this date we can say that the incidence of febrile seizures can be decreased by the correction of iron deficiency anemia in our population.

CONCLUSION

Children with febrile seizures were having significantly lower levels of hemoglobin, MCV, MCHC and plasma ferritin as compared to the control groups. This suggests that there is positive role of iron deficiency in the pathogenesis of febrile seizures. But to establish these findings on a solid ground a larger multi-centric study is needed.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Sherjil A, Saeed Z, Shahzad S, Amjad R. Iron Deficiency Anaemia- A Risk Factor for Febrile Seizures in Children. *J Ayub Med Coll Abbottabad* 2010; 22: 71-3.
2. Ullah I, Zahid M, Sthanadar AA, Sthanadar IA, Ali PA, Khan MI, et al. Iron Deficiency Anemia in school Age Children in District Karak Khyber Pakhtunkhwa Province, Pakistan. *OJBD*. 2014; 4(2): 9-14
3. Ohls RK, Christensen RD. Iron-Deficiency Anaemia. In: Kleigman M, Behrman E, Jenson B, Stanton F, editors. *Nelson Text book of Pediatrics*.18th Ed. Philadelphia: Saunders; 2008. p. 2014-7.
4. Khan SHM, Sohail M, Ali A, Akhtar N, Khan H, Rasool F. Symptoms- Based Evaluation of Iron Deficiency Anemia in Students of Bahawalpur Correlated with their Eating Habits. *Troop J Pharm Res* 2014; 13(5): 769-72.
5. Ambruso DR, Hays T, Goldenberg NA. Iron Deficiency Anaemia. In: William W. Hay, Jr, Myron J. Levin, Judith M, Robin R, editors. *Current Diagnosis and Treatment- Paediatrics* 19th ed. Denver: McGraw-Hill; 2009. p. 810-11.
6. Graves RC, Oehler K, Tingle LE. Febrile seizures: risks, evaluation, and prognosis. *Am Fam Physician* 2012; 85: 149-53.
7. Susan A, Zarrin-Taj KD, Mostafa A, Amin S, Zohreh K, Shahla A, et al. Relationship between Iron Deficiency Anemia and Febrile seizures. *Iran J Child Neurology* 2010; 4: 27-30.
8. Modaresi M, Mahmoudian T, Yaghini O, Kelishadi R, Golestan H, Tavasoli A, et al. Is Iron Insufficiency Associated With Febrile Seizure? Experience in an Iranian Hospital. *J Compr Ped* 2012; 3: 21-4.
9. Zareifar S, Hosseinzadeh HR, Cohan N. Association between iron status and febrile seizures in children. *Seizure* 2012; 21: 603-5.
10. Sadeghzadeh M, Khoshnevis Asl P, Mahboubi E. Iron status and febrile seizure- a case control study in children less than 3 years. *Iran J Child Neurol* 2012; 6: 27-31.
11. 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: 226-9.
12. Habibian N, Alipour A, Reianzadeh A. Association between Iron Deficiency Anemia and Febrile Convulsion in 3 to 60 Month Old Children: A Systematic Review and Meta-Analysis. *Iran J Med Sci* 2014; 39(6): 496-505.
13. Wang B, Zhan S, Gong T, Lee L. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. *Cochrane Database of Systematic Reviews*. 2013, Issue Jun 6;(6).Art. No.:CD001444.
14. Akhtar S, Ghaffar F. Prevalence of Anemia in Under five-year-old Children in he Kuwait Teaching hospital Peshawar, Khyber Pakhtunkhwa. *PUTAJ Humanities and Social Sciences*. 2014; 21(2): 165-71.
15. Johnston VJ. Seizures in Childhood. In: Kleigman M, Behrman E, Jenson B, Stanton F, editors. *Nelson Text book of Pediatrics*. 18th ed. Philadelphia: Saunders; 2009. p.1994-5
16. Khalid N, Abdurrahman, Akrem M. The association between iron deficiency anaemia and first febrile seizures. *Duhok Med J* 2010; 4: 60-6.

17. 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: 420-6.
 18. 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: 17-9.
 19. Bidabadi E, Mashouf M. Association between iron deficiency anemia and first febrile convulsion: A case-control study. *Seizure* 2009; 18: 347-51.
 20. Kobrinsky NL, Yager JY, Cheang MS. Does iron deficiency anemia raises seizure threshold? *J Child Neurol* 1995; 10: 105-9.
 21. Pisacane A, SansorR, Impigliazzo N. Iron deficiency anemia and febrile convulsion: a case control study in children under 2 yrs. *BMJ* 1996; 313: 343-5.
 22. Looker AC, Dallman PR, Carroll MD. Prevalence of iron deficiency in the United States. *JAMA* 1997; 277: 973-6.
 23. Ghasemi F, Valiadeh F, Taee N. Iron Deficiency Anemia in Children with Febrile Seizure: A Case-Control Study. *Iran J Chil Neurol* 2014; 8(2): 38-44.
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