

ASSOCIATION OF IRON DEFICIENCY ANEMIA IN CHILDREN WITH FEBRILE CONVULSIONS

Dr. Vikash Lal¹, Dr. Haresh Kumar², Dr. Shahina Hanif³, Dr. Om Parkash⁴, Dr. Suneel Arwani⁵

¹ Civil hospital, Dow University of Health Sciences, Karachi, Pakistan.

² Institute of Psychiatry, Baqai Medical University, Karachi, Pakistan.

³ Civil hospital, Dow University of Health Sciences, Karachi, Pakistan.

⁴ Liaquat University of Medical and health Sciences, Jamshoro, Pakistan.

⁵ Isra University Hyderabad, Pakistan.

Correspondence address: Dr. Haresh Kumar, Consultant Psychiatrist, Institute of Psychiatry, Baqai Medical University, Karachi, Pakistan. Email: hareshmakhija@gmail.com

Date of submission: April 29, 2016 **Date of revision:** May 27, 2016 **Date of acceptance:** July 25, 2016

ABSTRACT

Objective: To determine the association of iron deficiency anemia in children presented with febrile convulsion. **Study Design:** Case control study **Setting:** The pediatric unit III, Civil Hospital, Karachi. **Duration:** Six months from 30th April 2013 to 1st November 2013 **Material and Methods:** History regarding age, sex, developmental milestones, family history of febrile seizures or epilepsy, mean of the temperature peak at admission, and the underlying illness were recorded for all cases and controls, as well as details of seizure history, duration and frequency. Blood samples were collected in the Paediatric wards for measurements of hemoglobin, serum ferritin, MCV, MCH and MCHC, serum electrolytes, serum calcium, and serum blood sugar. If child with febrile seizures was <12 months then CSF analysis was done to rule out meningitis, with consent from parents/guardian, while in older children signs of meningeal irritation were checked. **Results:** There were overall 47.1% male and 52.9% female patients. In control group 28.6% were male and 71.4% were female patients. In cases group 65.5% were male and 34.5% were female patients. The overall mean age of study subjects was 34.9±9.3 months, with range of 52 (7–59) months. In control group the mean age was 35.27±9.11 month with range 50, mean weight was 13.13±2.55 Kg with range 12 (7–19) Kg, mean hemoglobin level was 9.97±0.29 g/dl with range 1.5 (9.2–10.7) g/dl, mean MCV score was 65.84±1.97 fl with range 10.0 (63.0–73.0) fl, mean MCH score was 27.84±1.97 Pg with range 10.0 (25.0–35.0) Pg, mean MCHC score was 28.84±1.97 gm/dl with range 10 (26.0–36.0) gm/dl, and mean Serum Ferritin Level was 30.84±1.97 fl with range of 10 (28.0–38.0) fl. In cases group the mean age was 34.53±9.49 month with range 51(7–58) months, mean weight was 12.80±2.64 Kg with range 11 (7–18) Kg, mean hemoglobin level was 10.00±0.30 g/dl with range 1.7 (9.2–10.9) g/dl, mean MCV score was 65.47±2.14 fl with range 13.0 (60.0–73.0) fl, mean MCH score was 27.43±2.11 Pg with range 12.0 (23.0–35.0) Pg, mean MCHC score was 28.45±2.09 gm/dl with range 12 (24.0–36.0) gm/dl, and mean Serum Ferritin Level was 30.45±2.10 fl with range of 12 (26.0–38.0) fl. Out of total 510 included patients iron deficiency anemia was observed in 133 patients among them 51 were in control group and 82 were in cases group. It was observed that there was significant association found between iron deficiency anemia and the two groups with p≤0.05 level of significance. Furthermore, odds ratio of 1.608 indicated that patients with cases are more likely to be diagnosed with Iron Deficiency Anemia. **Conclusion:** Children with febrile seizures are almost likely to have iron deficiency anemia. Iron deficiency anemia can be regarded as a risk factor that predisposes to febrile seizures in children.

Keywords:

Iron Deficiency, Iron Deficiency Anemia, Febrile Convulsions, Febrile Seizures

INTRODUCTION

Febrile convulsion (FC) is the most common seizure disorder affecting children between the age of 6 months and five years, without central nervous system infection. This condition affects 2.5% of the children, the peak age of FC occurrence is considered 14-18 months (¹⁻³). Febrile seizure have been studied extensively over the past decades, the precise cause of

FC is not known but several risk factors were identified which included; height of temperature over 38.5 °C, genetic and environmental factors (⁴). Studies reported that iron deficiency anemia could be a risk factor for FC, because the ages range of occurrence of both conditions are same (⁵). Nutritional deficiency among children is a global issue especially in developing countries (⁶). Iron deficiency anemia is found to be the most common nutritional deficiency in children.

46-66% of children less than 4 years of age are anemic and 50% of them have iron deficiency anemia in developing countries. Prevalence in Pakistan is nearly 65% (7-8). Iron has a key role in the transport of oxygen to different tissues such as brain and also an important player in the metabolism of some neurotransmitters and enzymes such as mono-amine-oxidase and aldehyde oxides (9). Evidence suggested that iron deficiency stimulates the function of neurons and consequently increase the risk of seizure. Association between FC and anemia does exist; however studies reported controversial results (10). Several studies suggested that febrile convulsion is found higher in patients with iron deficiency than in control group (11-12). Other studies reported opposite findings; they concluded that risk of FC in anemic children seems to be less as compared to children without iron deficiency anemia (13). Some studies suggested no role of iron deficiency in febrile convulsion in children (14-15). Apart from contradictory results regarding association of FC with anemia, most studies have shown that iron deficiency anemia was associated with febrile convulsion. Considering the fact that iron deficiency anemia is a risk factor for febrile convulsion, as well as lack of adequate data from past studies, the present study is carried out to determine the association of iron deficiency anemia in Pakistani children presenting with febrile convulsion.

METHOD

Sample size:

Taking frequency of iron deficiency in children with febrile seizures as 31.85% and in controls 19.6%, 95% confidence interval, 80% power, the sample size is 509 approximately 255 each in cases and controls.

Sample technique:

Non-probability consecutive sampling technique.

Study Design:

Case control study matched

SAMPLE SELECTION

Inclusion criterion: (Cases)

- Age 9 months to 5 years, either sex.
- Febrile convulsion.

Inclusion criteria: (Controls)

- Age 9 months to 5 years, either sex.
- No history of convulsion.

Exclusion criteria:

Following patients will be excluded from the study:

- Patients as already having Epilepsy
- Malnourished children
- Patients already on iron therapy
- Patients with developmental delay
- Patients with chronic hemolytic anemia
- Neurological infections (meningitis, encephalitis)
- Severely sick child
- Rickets
- Acute gastroenteritis (electrolyte imbalance)

DATA COLLECTION PROCEDURE:

This study was conducted in the pediatric unit III civil Hospital, Karachi, after taking approval from the ethical review committee. Patients, who fulfilled the inclusion criteria, included in the study. Informed consent has taken from parents. History taken from parents regarding age, sex, developmental milestones, family history of febrile seizures or epilepsy, the mean of the temperature in centigrade peak at admission, and the underlying illness recorded for all cases and controls, as well as details of seizure history, duration, frequency. After taking informed consent from parents blood samples were collected in the Paediatric wards, and then sent to the Pathology Department of hospital for measurements of hemoglobin, serum ferritin, MCV, MCH and MCHC, serum electrolytes, serum calcium, and serum blood sugar. In children with febrile seizures less than 12 months of age, CSF analysis was performed to rule out meningitis after taking consent from parents, while in older children signs of meningeal irritation were checked. The data recorded on pre-designed proforma by the researcher.

DATA ANALYSIS:

Data was analyzed on SPSS version 20. Descriptive statistics used to analyze and describe data. Frequencies and percentages were calculated for categorical (qualitative) variables like sex and age in cases and controls. Mean \pm SD were calculated for numerical (quantitative) variables like age, weight, hemoglobin level. Qualitative variables were presented in the form of tables and charts bar and pie charts). Keeping 95% confidence interval, the odds ratio was calculated from the data of cases and control. Chi square test was also applied. Regarding iron deficiency anemia $P \leq 0.05$ was considered as significant.

RESULTS:

Total 510 patients were evaluated to determine the association of iron deficiency anemia in children with febrile convulsions. The patients were divided into two groups, i.e. cases and control. Cases were defined as children with febrile illnesses (Fever $\geq 102^{\circ}\text{F}$), who were hospitalized with a convulsion that fulfills criteria for febrile seizure and controls are defined as age and gender matched children, with Fever $\geq 102^{\circ}\text{F}$, febrile illness but without any history of seizures. The overall mean age of study subjects was 34.9 ± 9.3 months, with a range of 52 (7 – 59) months. In control group 28.6% were male and 71.4% were female patients. In cases group 65.5% were male and 34.5% were female patients. These results are also presented in Table-1.

TABLE:1 Frequency Distribution by Gender

		Frequency (n)	Percentage (%)
Overall	Male	240	47.1%
	Female	270	52.9%
	Total	510	
Control Group	Male	73	28.6%
	Female	182	71.4%
	Total	255	
Cases Group	Male	167	65.5%
	Female	88	34.5%
	Total	255	

In control group the mean age was 35.27 ± 9.11 month with range 50 (9–59) months. Mean weight was 13.13 ± 2.55 Kg with range 12 (7–19) Kg. The mean hemoglobin level was 9.97 ± 0.29 g/dl with range 1.5 (9.2–10.7) g/dl. The mean MCV was 65.84 ± 1.97 fl with range 10.0 (63.0–73.0) fl. The mean MCH was 27.84 ± 1.97 Pg with range 10.0 (25.0–35.0) Pg. The mean MCHC was 28.84 ± 1.97 gm/dl with range 10 (26.0–36.0) gm/dl. The mean Serum Ferritin Level was 30.84 ± 1.97 fl with range of 10 (28.0 – 38.0) fl. The detailed descriptive statistics of these quantitative variables are presented in Table-2.

TABLE:2 Descriptive Statistics of Weight, Hb, MCV, MCH, MCHC, and Serum Ferritin According to CONTROL Group

	Mean	SD	Range	Minimum	Maximum
Age (months)	35.27	9.11	50	9	59
Weight (Kg)	13.13	2.55	12	7	19

Hemoglobin (g/dl)	9.977	0.293	1.5	9.2	10.7
MCV (fl)	65.84	1.97	10	63	73
MCH (Pg)	27.84	1.97	10	25	35
MCHC (gm/dl)	28.84	1.97	10	26	36
Serum Ferritin (fl)	30.84	1.97	10	28	38

In cases group the mean age was 34.53 ± 9.49 month with range 51 (7–58) months. Mean weight was 12.80 ± 2.64 Kg with range 11 (7–18) Kg. The mean hemoglobin level was 10.00 ± 0.30 g/dl with range 1.7 (9.2–10.9) g/dl. The mean MCV score was 65.47 ± 2.14 fl with range 13.0 (60.0–73.0) fl. The mean MCH score was 27.43 ± 2.11 Pg with range 12.0 (23.0–35.0) Pg. The mean MCHC score was 28.45 ± 2.09 gm/dl with range 12 (24.0–36.0) gm/dl. The mean Serum Ferritin Level was 30.45 ± 2.10 fl with range of 12 (26.0 – 38.0) fl. The detailed descriptive statistics of these quantitative variables are presented in Table-3.

TABLE:3 Descriptive Statistics of Weight, Hb, MCV, MCH, MCHC, and Serum Ferritin According to CASES Group

	Mean	SD	Range	Minimum	Maximum
Age (months)	34.53	9.49	51	7	58
Weight (Kg)	12.80	2.64	11	7	19
Hemoglobin (g/dl)	10.00	0.30	1.7	9.2	10.9
MCV (fl)	65.47	2.14	13	60	73
MCH (Pg)	27.43	2.11	12	23	35
MCHC (gm/dl)	28.45	2.09	12	24	36
Serum Ferritin (fl)	30.45	2.10	12	26	38

Out of total 510 included patients iron deficiency anemia was observed in 133 patients, the frequency distribution is presented in Table-4

TABLE:4 Frequency Distribution of Iron Deficiency Anemia

		Frequency (n)	Percentage (%)
Overall	Yes	133	26.1
	No	377	73.9
	TOTAL	510	

To find out the association between Iron Deficiency Anemia with Febrile Seizures chi square test was applied considering $p \leq 0.05$ as significant, with iron deficiency anemia in control and cases groups. It was observed that there was significant association found between iron deficiency anemia and the two groups with $p \leq 0.05$ level. Furthermore, odds ratio of 1.608 indicated that patients with cases are more likely to be diagnosed with Iron Deficiency Anemia. The detailed results are presented in Table-5.

TABLE:5 Frequency and Association of Iron Deficiency Anemia with Control and Cases Groups

		Iron Deficiency Anemia		P-value	ODD Ratio
		Yes	No		
Control	n	51	204	0.002*	0.848
	%	20.0%	80.0%		
Cases	n	82	173		1.608
	%	32.2%	67.8%		
TOTAL		133	377		

*Level of significance at 0.05

Odd Ratio = 1.608 (Patients with cases are more likely to be diagnosed with Iron Deficiency Anemia)

DISCUSSION

Iron has an important role in the metabolism and functioning of enzymes required in neurochemical reactions. It has been observed that iron deficiency is associated with many neurological symptoms such as learning difficulties, poor attention and memory, behavioral changes and influence normal developmental processes (16-17). Association between iron deficiency and febrile seizures was first evident in mid 90's in an Italian study (18). According to our results, 82 (32.2%) patients in the case and 51 (20%) in the control group had anemia, revealing significant relationship. In accordance with our results, a study carried out by Hartified and Colleagues in 2009 showed that, children with febrile seizures were twice as likely to have iron deficiency as compared to children with

normal iron studies (19). Pisacane et al also reported significantly high frequency of anemia in their cases (30%) as compared to control group (14%) (18). On the same lines, in 2001 Naveed-ur-Rehman and Colleagues conducted a study with 30 children with FC and 30 controls and they found significant higher rate of IDA in case group as compare to control group (20). Iron deficiency anemia was found in 20% in case group and 12% in control group in study done by Siadati (21). On the other hand, some studies have reported contradictory results regarding association of iron deficiency anemia and febrile seizures such as Kobrinsky et al. Found less iron deficiency in the case group and suggested that iron deficiency may play a protective role against febrile seizures (22). In another study by Bidabadi and Mashouf concluded that iron deficiency anemia in febrile convulsion group was less frequent than in controls, but found no protective effect of iron deficiency against febrile convulsions (23). Momen and Hakimzadeh found no relationship between febrile convulsion and iron deficiency anemia (24). The difference may be attributed to using different diagnostic criteria of IDA, difference of samples and ignoring the effect of age on interpretation of the tests for diagnosis of ID. Although our study has clearly indicated a cause-effect relationship between iron deficiency and first febrile seizure, however this should be appreciated that iron deficiency is much more frequent among hospitalized children of developing countries like Pakistan than developed world. Therefore large community based studies are needed in respect of association of two commonly prevalent medical conditions. In present study more iron status components (ferritin, Hb, MCV, MCH, MCHC) among cases and controls were also measured. We found that the mean ferritin level, Hb, and MCH in the FS group were significantly lower than the corresponding levels in the control group. There were no significant differences in other measures of iron status components, such as MCV and MCHC between cases and controls. Another finding of interest was that in our study sample, the prevalence of iron deficiency anemia ranged from 20% to 32%, whereas in most Western studies it is mentioned as 8% to 10%. Therefore, we also recommend an emphasis on screening and treatment of iron insufficiency in children in general.

CONCLUSION

Children with febrile seizures are more likely to have iron deficiency anemia. Iron deficiency anemia can be regarded as a risk factor that predisposes to febrile seizures in children. Low serum ferritin levels may play a role in the pathogenesis of simple febrile seizure.

Further studies, particularly in developed countries with a high frequency of Febrile Seizures and good nutritional conditions, are clearly needed.

References

- 1- Talebian A, Momtazmanesh N. Febrile Seizure and Anemia. *Iran J Child Neurology*. 2007;31-33.
- 2- Aicardi J. Febrile convulsion in epilepsy in children, 5th ed, Lippincot: William & Wilkins; 2004.220-34.
- 3- Wolf PS, Shinnar S. Febrile seizures in current management in child neurology. 2th ed, Hamilton: London;2002.960-96.
- 4- Shinnar S. Febrile seizure in Swaiman pediatric neurology. Principles and practice. 4th ed, Mosby;2006.1079-86.
- 5- Jonston MV. Febrile seizure, In Nelson text book of pediatrics, 17th ed. USA: Saunders; 2004.1992.
- 6- Martorell R. The nature of child malnutrition and its long-term implications. *Food & Nutrition Bulletin*. 1999; 20(3): 288-92.
- 7- Bidabadi E and Mashouf M. Association between iron deficiency anemia and first febrile convulsion. *Seizure*.2009; 18(5): 347-51.
- 8- Stoltzfus RJ. Defining iron-deficiency anemia in public health terms: a time for reflection. *The Journal of Nutrition*. 2001; 131(2): 565S-67S.
- 9- Pisacane A, Sanson R, Impagliazzo N. Iron deficiency anemia and febrile convulsion. *Br Med J*. 1999;313(7153):343.
- 10- Mo`omen A, Hakimzadeh M. Association between anemia and febrile seizure , A case-control study, *Ahwaz Uni Med Sci J*. 2002;35:50-4.
- 11- Ur-Rehman N, Billoo AG. Association between Iron Deficiency Anemia and Febrile Seizures. *J Coll Physicians Surg Pak*. 2005;15(6):338-40. [PubMed]
- 12- 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. *Iran J Child Neurol*. 2010;4(2):45-50.
- 13- Talebian A, Momtazmanesh N. Febrile Seizures and Anemia. *Iran J Child Neurol*. 2007;31-3.
- 14- SalehiOmran MR, Tamaddoni A, Nasehi MM, Babazadeh H, AlizadehNavaei R. Iron Status in Febrile Seizure: A Case-control Study. *Iran J Child Neurol*. 2009;3(3):40-3.
- 15- Amirsalari S, Keihanidost Z, Ahmadi M, Sabouri A, Kavemanesh Z, Afshar P, et al. Relationship between Iron Deficiency Anemia and Febrile Seizures. *Iran J Child Neurol*. 2010;14(1):27-30.
- 16- Ohls RK, Christensen RD. Iron-Deficiency Anaemia. *Nelson Text book of Pediatrics*.18th Ed. Philadelphia: Saunders; 2008.2014-7.
- 17- Ambruso DR, Hays T, Goldenberg NA. Iron Deficiency Anaemia. *Current Diagnosis and Treatment- Paediatrics*. 19th Edition. Denver USA: McGraw Hill; 2009.810-11.
- 18- 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. *Br Med J*. 1996;313(7053):343.
- 19- Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, et al. The association between iron deficiency and febrile seizures in childhood. *ClinPediatr (Phila)*. 2009;48:420-6.
- 20- Naveed-ur-Rehman, Billoo AG. Association between iron deficiency anemia and febrile seizures. *J Coll Physicians Surg Pak*. 2005;(6)338-40.
- 21- Siadati A, Sabooni F, Farivar S. Febrile seizure and serum iron level, abstracts book of 15th international congress of pediatrics Tehran, October 2003:151-3.
- 22- Kobrinsky NL, Yager JY, Cheang MS, Yatscoff RW, Tenenbein M. Does iron deficiency raise the seizure threshold? *J Child Neurol*. 1995;10(2):105-9.
- 23- Bidabadi E, Mashouf M. Association between iron deficiency anemia and first febrile convulsion: A case-control study. *Seizure*. 2009;18(5):347-51.
- 24- Momen AA, Hakimzadeh M. Case-control study of the relationship between anemia and febrile convulsion in children between 9 months and 5 years of age. *Sci Med J Ahwaz Uni Med Sci*. 2003;1(4):50-4.

Conflict of interest: Author declares no conflict of interest.

Funding disclosure: Nil

Author's contribution:

VikashLal: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Hareesh Kumar: data collection, data analysis, manuscript writing, manuscript review

ShaheenaHanif: Study concept and design, data analysis, manuscript writing, manuscript review

Om Parkash: data analysis, manuscript writing, manuscript review

SuneelArwani: Study concept and design, data analysis, manuscript writing, manuscript review