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Iron deficiency anemia as a risk factor for simple febrile seizures

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ABSTRACT

OBJECTIVE: To determine the association of iron deficiency anemia with simple febrile seizures in children presenting in a tertiary care hospital.

DESIGN: Case controls study.

Place & duration of study: Department of Pediatric Neurology, The Children's Hospital and Institute of Child health, Lahore, Pakistan from June 1, 2012 to May 31, 2013.

SUBJECTS & METHODS: A total 400 (200 cases & 200 controls) were included in the study. Children with febrile seizures and controls were included without seizures. Informed consent was taken from parents of each child. Children were divided into two groups, cases and controls, on the basis of presence or absence of seizures. Serum ferritin level, Hb, HCT and MCV levels were assessed.

RESULTS: Mean Hb level in cases and controls were 9.86 ± 2.28 and 9.48 ± 1.86 mg/dl respectively. Mean RDW among cases and controls was 28.82 ± 10.78 and 31.10 ± 15.97 . Mean MCV value in cases and controls was 69.03 ± 10.84 and 72.91 ± 11.63 respectively. Mean HCT level in cases was 29.75 ± 5.22 and in controls mean HCT level was 32.85 ± 11.86 . Among cases 93(46.5%) children and among controls 56(28%) children had iron deficiency anemia. Odds ratio of 2.235 shows that cases i.e. children who had iron deficiency anemia had 2.235 more chances of seizures as compared to children without anemia.

CONCLUSION: Iron deficiency anemia is considered as a risk factor for febrile seizures in children. (Cases vs controls 46.5% vs. 28%)

KEY WORDS: Iron deficiency anemia, Simple febrile seizures, Hemoglobin,

INTRODUCTION:

Febrile seizures (FS) are the commonest cause of seizures in children, occurring in 2-5% of children with lots of burden on health care system and cause of anxiety for parents.¹ Febrile Seizures episodes also cause a great deal of agony and psychological trauma to parents. About 2-7% of children who develop FS proceed to develop epilepsy later in life.²

Iron deficiency is the commonest micro nutrient deficiency worldwide, and is a preventable and treatable condition.³ Iron deficiency is ranked at the top of three global "hidden hungers" (Iron, Iodine, Vitamin A: sub-clinical deficiency without visible signs of deficiency) with about one fifth of world's population children in the developing world, iron is the most common single-nutrient deficiency.⁵

In Pakistan, prevalence of IDA is very high. According to National Nutrition Survey of Pakistan 2011, 33.4%

children are suffering from IDA at national level.⁶ Iron is needed for brain energy metabolism, for metabolism of neurotransmitters and for myelination. A lack of sufficient iron intake may significantly delay the development of the central nervous system as a result of alterations in morphology, neurochemistry, and bioenergetics.⁷

Various studies showed that iron Deficient children have more likelihood of developing FS.⁸⁻¹⁰ In one study 31.85% children with FS had evidence of IDA as compared to 19.6% without FS and a strong association was obtained (p-value = 0.014). It was concluded that children with FS are almost twice as likely to have IDA as compared to children with a febrile illness without seizures. IDA can be regarded as a risk factor that predisposes to febrile seizures in children.¹¹ Instead of that. In some of the studies these findings have not been confirmed.¹²

Kumari, et al. wrote that iron deficiency is also a risk factor for febrile seizures in children 6 months to

three years of age showing a highly significant association between iron deficiency and febrile seizures. As expected, a family history of febrile seizures or epilepsy in first degree relatives was also linked to the occurrence of febrile seizures in these children. The findings are consistent with another recent case-control study from Kenya of children 3-156 months of age, which reported that iron deficiency is a risk factor for simple febrile seizures but not for other types of acute seizures.^{8,13}

There is a debate going on whether there is an association between iron deficiency and the risk for febrile seizures or not. Several studies suggest a positive correlation between iron deficiency and febrile seizures; the iron dependent metabolism of several neurotransmitters has been suggested as a possible mechanism for this association. Conversely, other studies have suggested a negative association or no association between iron deficiency and febrile seizures.¹⁴⁻¹⁶

According to one of local case control study, 31.85% of cases had iron deficiency anemia whereas, 19.6% of controls were found to have iron deficiency anemia.¹¹ These results suggest that iron deficiency anemia was less frequent among the cases with febrile convulsion, as compared to the controls, and there is not a protective effect of iron deficiency against febrile convulsions.¹²

Rationale of this study is to determine the association of iron deficiency anemia with simple febrile seizures in children presenting in a tertiary care hospital. Iron deficiency anemia has high prevalence in Pakistan and febrile seizures constitute a major burden of pediatric emergencies.

PATIENTS AND METHODS

To determine the association of iron deficiency anemia with simple febrile seizures in children presenting in a tertiary care hospital

Following operational definitions will be used. Simple febrile seizures are defined as brief (<15-minute) generalized seizures that do not recur during a 24-hour period in a febrile child (temp>100°C) who is otherwise neurologically healthy and without evidence of any neurologic abnormality before and after episode of seizures and without any metabolic disturbance.

Iron deficiency anemia was labeled as if Hb<10gm/dl, Hct<33%, RDW>17 and MCV<70fl in blood of febrile child. It was a case control study conducted at emergency and Neurology department of The Children's Hospital and The Institute of Child Health Lahore from January 1st, 2013 to September 20th 2013 with a sample size was of 400 children. There were 200 cases in each group is calculated with 80% power of test, 5% level of confidence and taking expected percentage of IDA i.e. 31.85% in cases and 19.6% in controls in children with simple febrile seizures

presenting in a tertiary care hospital. We used non-probability, purposive sampling technique for sample collection. Inclusion criteria was children aged 6 months to 5 years of either gender with febrile illness (temperature>100°C).

CASES: Children with Seizures (as per operational definition)

CONTROLS: Children without seizures

Exclusion criteria was children with atypical febrile seizures (on clinical examination), afebrile seizures (through history and medical record), children having signs of CNS infection (clinical examination and positive bacteria on CSF examination), children with other chronic illnesses e.g. liver disease (AST>40IU, ALT>40IU), kidney disease (creatinine>1.2gm/dl), Cardiac problems (through medical record and examination), h/o asthma, children already on iron therapy (through medical record)

After approval from hospital ethical committee, 400 children fulfilling the selection criteria was included in the study. Informed consent was taken from parents of each child. Demographic details (name, age, sex, weight and contact) were also being obtained. Children were divided into two groups, cases and controls, on the basis of presence or absence of seizures. Then blood sample was drawn by a staff nurse specially appointed for this job through a 5cc BD syringe. Blood samples were sent to the laboratory of the hospital for assessment of serum ferritin level, Hb, Hct and MCV level in the blood. Reports were retrieved and discussed with senior consultant pathologist. Iron deficiency anemia was labeled (as per operational definition). All this information was recorded on pre-designed proforma. Data was entered and analyzed through computer based software i.e. SPSS version 17. Mean and standard deviation was calculated for continues variables like age, weight, hemoglobin, hematocrit, MCV and ferritin level. Frequency, Multiple bar chart, Line chart and percentage was calculated for qualitative variables like gender and IDA. Odds ratio was calculated to see the association between iron deficiency anemia and simple febrile seizures. OR>1 was considered statistically significant.

RESULTS:

A total of 400 children were included in the study. 200 were cases and 200 were controls. Among cases mean age was 2.08±1.07 years. While among controls mean age was 3.21±1.69 years respectively. (Table-I) cases shows that there were 130 male and 70 female children while among controls there were 145 male and 55 female children. Among cases 155 children weight was <10 Kg and only 45 children weight was >10 Kg. While in controls only 175 children weight was <10Kg and 25 children's weight was >10Kg. Among

cases mean temperature was 101.28 ± 1.16 . Minimum and maximum temperature in cases was 100 and 103. Mean temperature among controls was 100.21 ± 0.40 . Minimum and maximum temperature among controls was 100 and 101 respectively. (Table-II) Mean Hb level in cases and controls was 9.86 ± 2.28 and 9.48 ± 1.86 mg/dl. Minimum Hb among cases and controls was 5.50 and maximum Hb was 13.50 and 13.30 respectively. (Table-III) Mean MCV value in cases and controls was 69.03 ± 10.84 and 72.91 ± 11.63 respectively. Minimum value of MCV among cases and controls was 15 and 86. Mean HCT level in cases was 29.75 ± 5.22 . Minimum and maximum level of HCT in cases was 20 and 38 while in controls mean HCT level was 32.85 ± 11.86 with minimum and maximum value of HCT as 28.50 and 80 respectively. Iron deficient anemia was defined as per operational definition. Among cases 93(46.5%) children and among controls only 56(28%) children had iron deficiency anemia. Among cases more children had iron deficiency anemia as compared to that of controls. Odds ratio of 2.235 shows that cases i.e. children who had seizure they had 2.235 more chances that will have iron deficiency anemia as compared to that of those children without seizure. All these results are statistically significant with odd ratio of 2.235 (1.475-3.386).

DISCUSSION:

Febrile convulsions are the ones that occur in the presence of fever with no evidence of underlying CNS infection based on history, clinical examination and relevant laboratory tests. Febrile convulsions occur in 2-5% of all children with a recurrence rate of 30-40%. Generally the children, 6 months to 5 years of age are more prone to this disease. However, age for peak incidence is 14 to 18 months which overlaps with that of iron deficiency anemia which is from 6 to 24 months.^{11,17,18}

In developing countries 46-66% of children less than 4 years of age are anemic and 50% of them have iron deficiency anemia. Its prevalence among the Pakistani children is nearly 65%.¹⁹ It is established that iron is a key player in various metabolic transactions, therefore, must be provided at sufficient levels to sustain the normal functioning of the body. Iron is also essential for enzymes involved in neurochemical reactions. However its deficiency can affect several organs and cause malfunctioning of different systems of the body including neurological symptoms like behavioral changes, poor attention span and hearing deficits in childhood.²⁰

Febrile convulsion is one of the most common childhood emergency presented in emergency rooms with a frequency of about 2-5% in America and Europe and 6-9% in Japan. It is slightly more common in males and the predominant age for seizures in children is found to be between 6 months to 5 years.²¹

Factors increasing the risk of recurrence are a family history of febrile convulsions, first attack at the age less than 12 months, and the intensity and duration of the fever. Iron deficiency is one of the most prevalent nutrition associated clinical problems in the world. Emerging data from various studies reflects that 2.5-5 billion people including infants between 6 and 24 months of age are affected with this disorder. In a number of studies a possible association of iron deficiency and febrile seizures has been reported.^{22,23}

In this study mean age of cases and controls was 2.08 ± 1.07 and 3.21 ± 1.69 years. While gender distribution shows that among cases there were 130 male and 70 female children while among controls there were 145 male and 55 females. Overall male children were dominating females in this study. In contrast, some studies show contradiction to our findings and those cited elsewhere. Bidabadi et al found that mean age of the cases was 22.86 (months) while that of control was 21.91 months. On the similar grounds, the studies of Susan et al show evidence of divergent results as compared to our findings; the mean age of cases was found to be 39 months and the mean age of controls was 35 months.²⁴

According to the results of a local case control study in which association between iron deficiency anemia and febrile seizures in children was determined. Results of the study shows that 31.85% of cases (50 out of 157) had iron deficiency anemia whereas, 19.6% of controls (30 out of 153) were found to have iron deficiency anemia as revealed by low levels of hemoglobin level, serum ferritin level, mean corpuscular hemoglobin concentration and mean corpuscular volume. Odds ratio was 1.93.^{11,25} These results are consistent with the results reported by Sherjil A. However Odds Ratio of this study was higher as that of reported by Sherjil A as well as percentage of iron deficiency anemia was also high.¹²

Results of an Iranian case control study showed iron deficiency anemia as 44% in cases and 48% in controls. These results suggest that iron deficiency anemia was less frequent among the cases with febrile convulsion, as compared to the controls, and there is not a protective effect of iron deficiency against febrile convulsions.¹² Results of this study are contradicting to the results reported by Bidabadi E. An Indian case control study showed iron deficiency anemia among cases as 63.6% and 24.7% among controls with an Odds ratio of 5.34(3.27-8.73). Keeping these findings in mind the author concluded that Iron deficiency is a significant risk factor for simple febrile seizures in children of age group 6 months to 3 years.^{8,25}

An Indian case control study showed iron deficiency anemia among cases as 63.6% and 24.7% among controls with an Odds ratio of 5.34(3.27-8.73). Keeping these findings in mind the author concluded that Iron deficiency is a significant risk factor for simple febrile seizures in children of age group 6 months to 3

years.^{8,26}

Results of local study from Rawalpindi and by Ghasem Miri-Aliabad are similar to the results of this study. While Derakhshanfar H reported results are contradicted to the results of this study.^{11,27}

A recent study from Rawalpindi Pakistan determined the association of iron deficiency anemia with febrile seizures. Among cases 64% had low serum ferritin level while among controls 42% had low serum ferritin level.²⁸

Another Iranian study reported that iron deficiency anemia in 44.6% cases in contrast to 58.4% controls ($p < 0.016$).²⁹

Ghasem Miri-Aliabad from Iran in his study reported iron deficiency anemia as 44% and 36% among cases and controls.³⁰ Results of this study is consistent with the results of Indian study but Odds ratio reported by Indian study was high than that of this study. i.e. 5.34 and in this study.^{12,31}

To conclude, it becomes important to evaluate iron deficiency anemia among children who had febrile seizures to prevent immediate complications, public health burden and cost of medical care bear either by parents and government. Among developing countries, anemia is more prevalent among children with febrile seizures. Moreover, iron plays an important role in normal brain development and metabolism; consequently its down regulation may halt many substantive physiological functions and could lead to initiation of febrile convulsions.

CONCLUSION:

Iron deficiency anemia is considered as a risk factor for children with febrile seizures. Results shows twice the risk of iron deficiency anemia for children with febrile seizures. Treatment with oral iron therapy is cost effective and easy remedy to prevent further episodes of febrile seizures.

TABLE-I
AGE FOR CASES & CONTROLS
(age in years)

	Cases	Controls	Total
N	200	200	400
Mean	2.08	3.21	2.65
SD	1.07	1.69	1.52
Minimum	0.50	0.50	0.50
Maximum	4.00	5.00	5

TABLE-II
HEMOGLOBIN (gm/dl)
OF CASES & CONTROLS

	Cases	Controls	Total
N	200	200	400
Mean	9.86	9.48	9.67
SD	2.28	1.86	2.09
Minimum	5.50	5.50	5.50
Maximum	13.50	13.30	13.50

TABLE-III
CONTROLS
(Percent)

	Cases	Controls	Total
N	200	200	400
Mean	29.75%	32.85%	31.30
SD	5.22%	11.86%	9.28
Minimum	20.00%	18.50%	18.50
Maximum	38.00%	80.00%	80

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Tipu Sultan; concept, data collection, data analysis, manuscript writing, manuscript review

Abdul Islam Hanif; data collection, data analysis, manuscript writing, manuscript review

Shaila Ali; data analysis, manuscript writing, manuscript review