Original Article

ASSOCIATION OF FEBRILE SEIZURES AND IRON DEFECIENCY ANEMIA

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ABSTRACT:

BACKGROUND: Febrile seizures (FS) affect 3-4% of children under the age of 5 years. It is benign and has an excellent prognosis. Male children with family history of febrile seizures, low serum calcium, sodium & blood sugar and microcytic hypochromic anemia are more prone to FS. Iron deficiency has been postulated to contribute to FS as it has a key role in brain energy metabolism, myelination, long term behavioral changes and cognitive impairments.

PATIENTS AND METHODS: A case-control study was conducted in the Department of Pediatrics Allied Hospital, Faisalabad from December 2014 to November 2015. Forty five children with fever and seizures and 45 children with fever but no seizure, of age 6 months to 60 months, were recruited. Blood samples of the children were obtained. Serum ferritin and Mean Corpuscular Volume (MCV) levels were assessed. Iron deficiency was labeled at Serum ferritin <7 µg/L and MCV <65 fL. Data was entered and analyzed using SPSS v. 20.0.

RESULTS: 60% (n=27) of children with febrile seizures showed iron deficiency anemia out of which 59% (n=16) were males and 41% (n=11) were females and most of these children 48% (n=13) belonged to the age group of 13 to 30 months. Logistic regression analysis and p value showed iron deficiency to be significantly associated with febrile seizures. Odds ratio showed children with febrile seizures to be 6.93 times more prone to develop iron deficiency.

CONCLUSION: Febrile seizures are significantly associated with iron deficiency and the children with iron deficiency has about 6 times more chances of developing febrile seizures as compared to children with normal serum ferritin levels.

KEYWORDS: Febrile seizures, iron deficiency anemia, serum ferritin, children, pediatrics.

INTRODUCTION:

The most common form of pediatric seizures and one of the most frequently encountered pediatric emergencies is febrile seizure (FS). It affects 3-4% of children under the age of 5 years, with a peak in at 14-18 months of age. Globally, febrile seizure has an incidence rate of 4.8/ 1000 person/year with a higher rate in developing countries due to higher occurrence of infections and childhood fever. [1]

Febrile seizures are although recurrent but benign and have an excellent prognosis. It is essential to differentiate benign febrile seizures from epilepsy as acute as well as long term management and also the prognoses of the two conditions is different. Children who are males, with a family history of febrile seizures, have low serum calcium, sodium, blood sugar and microcytic hypochromic anemia and history of antenatal complications are more prone to undergo an episode of seizure when they develop acute peak body temperature with no known cause. [2] [3] Although minimal, but these

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children do have a risk of developing epilepsy later in life. [4]

Fact that the peak age of FS incidence (14 to 18 months) also corresponds to the peak age of incidence of iron deficiency anemia (6 to 24 months) first led to the idea that there might be an association between the two. [5]

Micronutrient deficiency, especially iron, already has a well-established role in a potential of long term behavioral changes and cognitive impairments such as altered attention span, low intelligence and disturbed emotions and behavior.[6] Iron is also required for brain energy metabolism and has a key role in neurotransmitter metabolism and myelination. Hence, iron deficiency is also postulated to reduce the seizure threshold.[7]

Some studies have shown a significant association of iron deficiency with occurrence and recurrence of febrile seizures[8,9] while some other studies failed to do so.[10] Literature review shows that previously certain controversies and ambiguities are prevailing regarding iron deficiency as a risk factor for development of febrile seizures. Hence, we conducted this study to find the association of iron deficiency anemia with febrile seizures in our setup.

MATERIALS AND METHODS:

It was a case-control cross sectional study conducted in the Department of Pediatrics Allied Hospital, Faisalabad between December 2014 and November 2015. Non-Probability, purposive sampling strategy was adapted. Children of age 6 months to 5 years admitted with complain of fever were invited to included in the study. Children with simple febrile seizure as per American Academy of Pediatrics (AAP) definition were included in the case group and children with febrile illness but no seizure were included in the control group. Each group had 45 children.

The AAP defines febrile seizure as a seizure of less than 15 minutes which is generalized and occurs within the first 24 hours of fever in a neurobiologically healthy child of age 6 months to 60 months. The first episode is termed as simple febrile seizure and when a child has multiple episodes it is called complex febrile seizure. [11]

Following children were included in the study:

- Children with parents who gave their informed consent.
- Children who allowed the investigators to draw their blood sample.
- Children of age 6 months to 60 months.
- Children having fever (body temperature of more than 38º centigrade) for more than 24 hours.

Following children were excluded from the study:

- Children with afebrile seizures
- Known cases of epilepsy
- Children with CNS infections such as meningitis, encephalitis
- Children with CNS malformations
- Children with history of birth asphyxia or developmental delay
- Children on supplemental iron
- Children with anemia other than iron deficiency
- Children with metabolic disorders or electrolytes imbalance
- Children with chronic multisystem diseases

The parents were requested to fill a questionnaire that included demographic details and history of illness of their children. A physical examination of the child was conducted. Blood samples of the children were obtained for assessment of serum ferritin and Mean Corpuscular Volume (MCV) levels. Iron deficiency was labeled at Serum ferritin level <7 micro-grams per liter (µg/L) and MCV <65 femtoliters (fL).

The collected data was entered and analyzed using SPSS version 20.0. Mean and standard deviation were calculated for quantitative variables like age, serum ferritin and MCV levels. Frequency and percentage were calculated for categorical variables like gender and iron deficiency. Odds Ratio (OR) was calculated to measure association between iron deficiency and febrile seizures. OR≥1 was considered as significant. Data was stratified for effect modifier like age and gender and chi square test was used to compare stratified groups. Logistic regression was applied to see impact of multiple factors i.e. age, gender and serum ferritin and MCV level. P-value≤0.05 was considered as significant.

RESULTS:

Forty five children were included in cases and 45 in controls of the 90 children, 60 were males (Cases=26, Controls=34) and 30 were females (Cases=19, Controls=11). Mean age of cases and controls (in months) was 30.60±16.36 and 36.58±14.62 respectively. The mean Serum ferritin level of the cases was 61.07±84.42 (ug/L) and that of controls was 162.31±97.32 (ug/L). Mean MCV level of the cases was 66.27±17.67fL with a range of 40-93 fL and that of controls was 83.11±13.75fL with a range of 51-96 fL.

60% of the cases (n=27) showed iron deficiency in comparison to 17.78%(n=8) of the controls and the difference was significant (p-value 0.000). Cases were 6.93 times more prone to develop iron deficiency (OR = 6.93). (Table I)

Table I: Iron Deficiency in cases and controls

		Cases n (%)	Controls n (%)	Total n (%)
Iron Deficiency	Yes	27(60%)	8(17.78%)	35 (40%)
	No	18(40%)	37(82.22%)	55 (60%)
Total		45 (100%)	45 (100%)	90 (100%)

*Chi-Square Test= 16.87 **p-value= 0.000 ***Odds Ratio= 6.93 (2.63-18.28)

The frequency of iron deficiency among the cases and controls and its relation to gender stratification with its statistical significance is shown in Table II.

Table II: Iron deficiency in cases and controls in relation to gender stratification

Iron Deficiency		Groups		Chi-Square Test	p-value
		Cases	Controls		
Male	Yes	16 (61.5%)	6 (17.6%)	12.22	0.000
	No	10 (38.5%)	28 (82.4%)		
Female	Yes	11 (57.9%)	2 (18.2%)	4.47	0.034
	No	8 (42.1%)	9 (81.8%)		

In our study, 26 (28.9%) children belonged to the age group of 0.5-1.0 years, 40 (44.5%) children belonged to the age group of 1.1-2.5 years, 8 (8.9%) children belonged to the age group of 2.6-3.0 years, 14 (15.5%) children belonged to the age group of 3.1-4.5 years and 2 (2.2%) children belonged to the age group of >4.5 years. The frequency of iron deficiency among the cases and controls and its relation to age stratification is shown in Table III.

Table III: Iron deficiency in cases and controls in relation to age stratification

Iron Deficiency		Cases n (%)	Controls n (%)	Chi-Square	p-value
0.5-1.0 Years	Yes	9 (56.3%)	1 (10%)	5.56	0.018
	No	7 (43.8%)	9 (90%)		
1.1-2.5 Years	Yes	13 (68.4%)	6 (28.6%)	6.35	0.012
	No	6 (31.6%)	15 (71.4%)		
2.6-3.0 Years	Yes	0 (0%)	1 (20%)	0.686	0.408
	No	3 (100%)	4 (80%)		
3.1-4.5 Years	Yes	5 (83.3%)	0 (0%)	10.37	0.001
	No	1 (16.7%)	8 (100%)		
>4.5 Years	Yes	0 (0%)	0 (0%)	-	-
	No	1 (100%)	1 (100%)		

Logistic regression analysis showed the impact of age, gender, serum ferritin level, serum MCV and Iron deficiency anemia in children with febrile seizures. In logistic regression model, odds ratio for age is OR= 1.010 (CI: 0.976-1.046), for gender it is OR=0.486 (CI: 0.168-1.411), for serum ferritin level is OR=1.001 (CI: 1.001-1.019), for MCV is OR=1.096 (CI: 0.994-1.209) and for iron deficiency anemia it is OR=0.065 (CI: 0.002-2.227) (Table IV).

Table IV: Impact of various variables on febrile seizures according to logistic regression

Variables	B	S.E.	Wald	df	Sig.	Exp(B)	CI (95%)	
Age (in months)	.010	.018	.344	1	.557	1.010	0.976	1.046
Gender	-.721	.543	1.760	1	.185	.486	0.168	1.411
Serum ferritin (µg/L)	.010	.005	4.351	1	.037	1.010	1.001	1.019
Serum MCV (fL)	.092	.050	3.367	1	.067	1.096	0.994	1.209
Iron deficiency anemia	-2.734	1.804	2.299	1	.129	.065	.002	2.227
Constant	-2.905	1.711	2.880	1	.090	.055		

**Logistic model: febrile seizure = -2.905 (constant) + 0.010 (age) – 0.721 (gender) + 0.010 (S. ferritin) + 0.092 (S. MCV) – 2.735 (iron deficiency anemia)*

DISCUSSION:

Our study shows 60% of children with febrile seizure (FS) have iron deficiency anemia (IDA). Most of these children are males and belong to the age group of 13-30 months and a mean age of 20.57 (±5.12) months.

Our findings correlate with existing literature that reports iron deficiency to be a risk factor for febrile seizure and coexistence of the two conditions in the same age group and role of iron in neurotransmitter metabolism and brain oxygenation.[12] Our results are comparable with other studies such as Fallah et al which reported a mean age of 22.78±11.08 months of iron deficient children experiencing FS; out of which more were boys.[13] Similarly another local study reports mean age of iron deficient children experiencing FS to be 27.90±14.60 months; with more frequency among boys.[9]

This association has been attracting the attention of researchers for more than a decade now. Many studies have supported the hypothesis and many results have shown a significant association between IDA and FS.[1,2,3,8,9,12]

However, even today some studies have reported contrary results. According to the results of Shah G et al, 23% cases vs 17% controls presented with IDA. Odds ratio and p value were both insignificant. Similarly, odds ratio for association of iron deficiency anemia with simple as well as complex febrile convulsion cases was greater than 1.[10] Derakhshanfar et al, reported that incidence of iron deficiency anemia was significantly higher in febrile children without seizures than children with FS ($p<0.016$).[14] Kobrinsky study reported febrile children with seizures to be less frequently iron deficient with higher hemoglobin, hematocrit and MCV than their controls. The study suggested iron deficiency anemia to be a protective factor against FS.[15] Talebian et al also quoted the lesser risk of FS in anemic children as compared to non-anemic ones.[16]

The literature is inconsistent whether iron deficiency anemia is a protective or a causative risk factor for febrile seizure in children and no one has postulated the substantial evidence to nullify the other. The possible reason of this discrepancy is the difference in genetic build up, neurobiological composition of individual child's brain, age, nutritional practices, geographic differences, sample size and characteristics of the control group.

CONCLUSION:

Thus it has been concluded through results of this study that febrile seizures are significantly associated with iron deficiency and the children with iron deficiency have about 6 times more chances of developing febrile seizures as compared to children with normal serum ferritin levels.

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