Original Research Article

Prevalence and association of iron deficiency anaemia in febrile seizures a prospective observational study

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Abstract

Background: Iron deficiency anemia and febrile seizure are two common conditions in children world wide as well as in our country. iron deficiency is known to cause neurological symptoms like behavioural changes, poor cognition and attention span thereby it may be associated with another common neurological condition in childhood like febrile seizure**.** **Materials And Methods:** Observational study , looking for the prevalence of iron deficiency anemia in cases of febrile seizures. A minimum sample size of 350 cases of typical febrile seizure in children in age group of 6 months to 60 months are taken with a prevalence of iron deficiency anemia in febrile seizure was around 31.85 % at a confidence interval of 95%. **Results:** Out of 350 children enrolled 131 (37.4%) were female and 219 (62.6%)were males. Out of the 350 children's 107 (30.6%)were found have associated iron deficiency anaemia, which included 64(59.8%) of male and 43 (40.2%) Of females. Peak incidence of Febrile Seizures found maximum between 13 to 18 months(39.4%). **Conclusion** : low serum iron levels and the presence of anemia can serve as strengthening factors for the Febrile seizures in children. Therefore, ID(Iron deficiency) can be added to the list of risk factors for febrile convulsions. Accordingly, children with FSs are suggested to be monitored for diagnosis and treatment of IDA. Furthermore, it is advisable to prescribe iron supplements earlier and more carefully to children who have important and well-known risk factors for febrile convulsion, such as family history of febrile convulsion.

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INTRODUCTION

Febrile convulsion (FC) is the most common disorder in the nervous system of children and 2-5% of the total number of (or 4.8 out of every 1000) children become affected every year.[1] Febrile convulsion is defined as convulsion resulting from fever. It occurs in children of 6 months to 6 (full six) years of age, is accompanied by fever higher than 38°C, and does not involve symptoms of central nervous system infections or any other background causes.[1] Risk factors of this disorder include history of convulsion or FC in the family, head injuries, mothers who smoke or consume alcoholic beverages, and high fevers.[2,3,4,5,6] Since a risk of FC is the probability of its subsequent development into convulsion and epilepsy, various studies have been carried out with the purpose of identifying correctable risk factors to reduce the prevalence of FC and, hence, of epilepsy and convulsion.

Aims and Objectives: To determine the relationship between iron deficiency anaemia and febrile seizures. To find out the incidence of anemia in febrile seizure in males and females. To identify the peak age group of febrile seizures.

MATERIALS AND METHODS

Febrile seizures will be associated with iron deficiency anemia in at least about 30% of cases.

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Source of study: The proposed study is a hospital based prospective observational study consisting of infants and children aged between 6 months to 5 years. They will be evaluated at Department of Paediatrics, Ayaan institute of medical sciences including both OP and IP cases.
Study duration: 01.10.2019 TO 01.10.2020. **Study Design:** Observational study, looking for the prevalence of iron deficiency anemia in cases of febrile seizures. **Sample Size:** A minimum sample size of 350 cases of typical febrile seizure in children in age group of 6 months to 60 months are taken with a prevalence of iron deficiency anemia in febrile seizure was around 31.85 % at a confidence interval of 95%. Sample size calculation for the present study was based on the case control study done by Sherjil A, US saeed Z, Shehzed S. Amjed R in which it was found 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 deficiency anaemia as revealed by low levels of haemoglobin level, serum ferritin level. Mean Corpuscular Haemoglobin Concentration and Mean Corpuscular Volume[15]. Odds ratio was 1.93." It was found that a minimum sample size required is 323. This was calculated using sample size for frequency in population on OpenEpi, version 3, open source calculator –SSPropor. However I am taking a sample size of 350 for better validation of results.
Sampling Method: Simple random sampling.
Inclusion Criteria: Children with typical febrile seizure between 6 months and 5 years.
Exclusion Criteria: Children aged < 6 months and > 5years. Children presenting with atypical febrile seizures. Children presenting with afebrile seizures or those having any signs of CNS infection. Those children with history of birth asphyxia/developmental delay/epilepsy. Those children on Iron supplementation therapy. Very sick children. Children those fall into Grade III PEM category on IAP charts. Family h/o Epilepsy/mental retardation.
Statistical Methods: Descriptive statistics, frequencies and percentages, chi square, SPSS window.

RESULTS

This study is a hospital based prospective observational study which includes 350 children in the age group of 6m to 60m with typical Febrile seizures. Out of 350 children enrolled 131 (37.4%)were female and 219 (62.6%)were males. Out of the 350 children's 107 (30.6%)were found have associated iron deficiency anaemia, which included 64(59.8%) of male and 43 (40.2%) Of females. Peak incidence of Febrile Seizures found maximum between 13 to 18 months(39.4%). And the Peak incidence of Febrile Seizures with Iron deficiency anaemia was found at 13m to 18 months and 25 to 36 months as 25.2% and 26.2% respectively. 1st episode of Febrile seizures was found to occur maximally during the age group of 13m to 18 months (51.1%). From the above data I conclude that there is a strong association between febrile seizures and iron deficiency Anaemia. (P <0.001).

Table 1: IDA1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	243	69.4	69.4	69.4
	Yes	107	30.6	30.6	100.0
	Total	**350**	**100.0**	**100.0**	

Table 2: IDA1 * sex Crosstabulation

			sex		Total
			F	M	
IDA1	No	Count	88	155	243
		% within IDA1	36.2%	63.8%	100.0%
		% within sex	67.2%	70.8%	69.4%
	Yes	Count	43	64	107
		% within IDA1	40.2%	59.8%	100.0%
		% within sex	32.8%	29.2%	30.6%
Total		Count	131	219	350
		% within IDA1	37.4%	62.6%	100.0%
		% within sex	100.0%	100.0%	100.0%

Table 3: Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.501[a]	1	.479		
Continuity Correction[b]	.345	1	.557		
Likelihood Ratio	.498	1	.480		
Fisher's Exact Test				.549	.278
Linear-by-Linear Association	.499	1	.480		
N of Valid Cases	350				

Table 4: IDA1 * Rage Crosstabulation

			Rage					
			6-12	13-18	19-24	25-36	37-48	49-60
IDA1	No	Count	27	111	39	58	5	3
		% within IDA1	11.1%	45.7%	16.0%	23.9%	2.1%	1.2%
		% within Rage	65.9%	80.4%	68.4%	67.4%	31.3%	25.0%
	Yes	Count	14	27	18	28	11	9
		% within IDA1	13.1%	25.2%	16.8%	26.2%	10.3%	8.4%
		% within Rage	34.1%	19.6%	31.6%	32.6%	68.8%	75.0%
Total		Count	41	138	57	86	16	12
		% within IDA1	11.7%	39.4%	16.3%	24.6%	4.6%	3.4%
		% within Rage	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 5: IDA1 * Rage Crosstabulation

			Total
IDA1	No	Count	243
		% within IDA1	100.0%
		% within Rage	69.4%
	Yes	Count	107
		% within IDA1	100.0%
		% within Rage	30.6%
Total		Count	350
		% within IDA1	100.0%
		% within Rage	100.0%

Table 6: Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	30.457[a]	5	.000
Likelihood Ratio	28.864	5	.000
Linear-by-Linear Association	15.263	1	.000
N of Valid Cases	350		

Table 7: Crosstab

			Rage				
			6-12	13-18	19-24	25-36	37-48
Episode	1	Count	14	23	3	4	1
		% within Episode	31.1%	51.1%	6.7%	8.9%	2.2%
		% within Rage	100.0%	85.2%	16.7%	14.3%	9.1%
	2	Count	0	4	15	15	4
		% within Episode	0.0%	9.1%	34.1%	34.1%	9.1%
		% within Rage	0.0%	14.8%	83.3%	53.6%	36.4%
	3	Count	0	0	0	9	6
		% within Episode	0.0%	0.0%	0.0%	50.0%	33.3%
		% within Rage	0.0%	0.0%	0.0%	32.1%	54.5%
Total		Count	14	27	18	28	11
		% within Episode	13.1%	25.2%	16.8%	26.2%	10.3%
		% within Rage	100.0%	100.0%	100.0%	100.0%	100.0%

Table 8: Crosstab

			Rage	Total
			49-60	
Episode	1	Count	0	45
		% within Episode	0.0%	100.0%
		% within Rage	0.0%	42.1%
	2	Count	6	44
		% within Episode	13.6%	100.0%
		% within Rage	66.7%	41.1%
	3	Count	3	18

	% within Episode	16.7%	100.0%
	% within Rage	33.3%	16.8%
Total	Count	9	107
	% within Episode	8.4%	100.0%
	% within Rage	100.0%	100.0%

Table 9: Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	82.880[a]	10	.000
Likelihood Ratio	95.110	10	.000
Linear-by-Linear Association	52.882	1	.000
N of Valid Cases	107		

Table 10

Crosstab

			sex		Total
			F	M	
Episode	1	Count	19	26	45
		% within Episode	42.2%	57.8%	100.0%
		% within sex	44.2%	40.6%	42.1%
	2	Count	17	27	44
		% within Episode	38.6%	61.4%	100.0%
		% within sex	39.5%	42.2%	41.1%
	3	Count	7	11	18
		% within Episode	38.9%	61.1%	100.0%
		% within sex	16.3%	17.2%	16.8%
Total		Count	43	64	107
		% within Episode	40.2%	59.8%	100.0%
		% within sex	100.0%	100.0%	100.0%

Table 11: Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.134[a]	2	.935
Likelihood Ratio	.134	2	.935
Linear-by-Linear Association	.097	1	.756
N of Valid Cases	107		

Table 12: Episode * IDA1 Crosstabulation

			IDA1		Total
			No	Yes	
Episode	1	Count	175	45	220
		% within Episode	79.5%	20.5%	100.0%
		% within IDA1	72.0%	42.1%	62.9%
	2	Count	58	44	102
		% within Episode	56.9%	43.1%	100.0%
		% within IDA1	23.9%	41.1%	29.1%
	3	Count	10	18	28
		% within Episode	35.7%	64.3%	100.0%
		% within IDA1	4.1%	16.8%	8.0%
Total		Count	243	107	350
		% within Episode	69.4%	30.6%	100.0%
		% within IDA1	100.0%	100.0%	100.0%

Table 13: Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	33.191[a]	2	.000
Likelihood Ratio	32.046	2	.000
Linear-by-Linear Association	33.082	1	.000
N of Valid Cases	350		

Table 14

Notes

Output Created		09-JUN-2016 16:52:02
Comments		
Input	Active Dataset	DataSet1
	Filter	<none>
	Weight	<none>
	Split File	<none>
	N of Rows in Working Data File	350
Missing Value Handling	Definition of Missing	User defined missing values are treated as missing.
	Cases Used	Statistics for each analysis are based on the cases with no missing or out-of-range data for any variable in the analysis.
	Syntax	T-TEST GROUPS=IDA1(1 2) /MISSING=ANALYSIS /VARIABLES=RBC HB PCV MCV MCH MCHC /CRITERIA=CI(.95).
Resources	Processor Time	00:00:00.03
	Elapsed Time	00:00:00.05

Table 15: Group Statistics

	IDA1	N	Mean	Std. Deviation	Std. Error Mean
RBC	No	243	4.721	.3363	.0216
	Yes	107	4.504	.3873	.0374
HB	No	243	12.270	.6964	.0447
	Yes	107	10.263	.8097	.0783
PCV	No	243	36.395	2.1913	.1406
	Yes	107	30.757	2.7467	.2655
MCV	No	243	77.300	4.2357	.2717
	Yes	107	68.423	3.4179	.3304
MCH	No	243	26.055	1.4828	.0951
	Yes	107	22.832	1.2028	.1163
MCHC	No	243	33.731	.7898	.0507
	Yes	107	33.416	1.1348	.1097

Table 16: Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means	
		F	Sig.	t	df
RBC	Equal variances assumed	.005	.946	5.320	348
	Equal variances not assumed			5.037	179.411
HB	Equal variances assumed	.091	.763	23.617	348
	Equal variances not assumed			22.278	178.020
PCV	Equal variances assumed	1.482	.224	20.467	348
	Equal variances not assumed			18.766	167.966

MCV	Equal variances assumed	19.517	.000	19.108	348
	Equal variances not assumed			20.751	248.133
MCH	Equal variances assumed	13.061	.000	19.793	348
	Equal variances not assumed			21.453	246.908
MCHC	Equal variances assumed	20.119	.000	2.981	348
	Equal variances not assumed			2.602	152.997

Table 17: Independent Samples Test

		t-test for Equality of Means			
		Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference
					Lower
RBC	Equal variances assumed	.000	.2177	.0409	.1372
	Equal variances not assumed	.000	.2177	.0432	.1324
HB	Equal variances assumed	.000	2.0078	.0850	1.8406
	Equal variances not assumed	.000	2.0078	.0901	1.8299
PCV	Equal variances assumed	.000	5.6381	.2755	5.0963
	Equal variances not assumed	.000	5.6381	.3004	5.0449
MCV	Equal variances assumed	.000	8.8772	.4646	7.9634
	Equal variances not assumed	.000	8.8772	.4278	8.0346
MCH	Equal variances assumed	.000	3.2229	.1628	2.9026
	Equal variances not assumed	.000	3.2229	.1502	2.9270
MCHC	Equal variances assumed	.003	.3144	.1054	.1070
	Equal variances not assumed	.010	.3144	.1208	.0757

Table 18: Independent Samples Test

		t-test for Equality of Means
		95% Confidence Interval of the Difference
		Upper
RBC	Equal variances assumed	.2981
	Equal variances not assumed	.3029
HB	Equal variances assumed	2.1750
	Equal variances not assumed	2.1856
PCV	Equal variances assumed	6.1798
	Equal variances not assumed	6.2312
MCV	Equal variances assumed	9.7909
	Equal variances not assumed	9.7197
MCH	Equal variances assumed	3.5431
	Equal variances not assumed	3.5188
MCHC	Equal variances assumed	.5218
	Equal variances not assumed	.5531

DISCUSSION

Iron deficiency anemia and febrile seizure are two common conditions in children worldwide as well as in our country. iron deficiency is known to cause neurological symptoms like behavioural changes, poor cognition and attention span. thereby it may be associated with another common neurological condition in childhood like febrile seizure. In the current study which is a hospital based prospective observational study where 350 children presented with typical febrile seizure in the age group of 6 months to 60 months were enrolled. out of which 131(37.5%) were females and 219(62.6%) were males. iron deficiency anemia was found to be associated with 30.6% of the subjects. Febrile seizure were found to be more prevalent in males (62.6%), in contrast in females(37.4%). Peak incidence of febrile seizure was found maximum (39.4%) at 13-18months. In accordance with our research, a Indian case control study by kumari *et al.* in 2012 suggested that highly significant association was found between iron deficiency and febrile seizure with crude odd's ratio of 5.34 and adjusted odd's ratio in the logistic regression analysis was 4.5with $p<0.001$.[4] Also in another Indian study, by vaswani *et al.*, in 2010 68% of cases were iron deficient compared to 30 % of controls indicating iron deficiency could be a potential risk factor for febrile seizure in children.[5] A study by pisacane *et al.* Reported that anemia in their case group (30%) was higher than in hospital control group (14%) and healthy group(12%).[06] A study by Ur-Rahman and Billoo on 30 children with febrile convulsion and 30 children with other

febrile illness indicated that iron deficiency anemia in their case group were significantly more common than in controls.[7] A Kenyan case control study as well as the meta analysis of 8 case control studies that have examined the relationship between febrile seizure and iron deficiency, suggested that iron deficiency may be associated with an increased risk of febrile seizure in children.[8]

Iron deficiency and iron deficiency anemia may play an important role in inducing seizures from the following mechanisms:[9]

Decrease in GABA inhibitory neurotransmitter due to change in its metabolism. Reduction of enzymes such as monoamine and aldehyde oxidases. Impairment in oxygenation and energy metabolism of the brain.

In a study conducted in Thailand, the rate of thalassemic children with febrile convulsion was reported as being 4.4% less than the general population of children. the researchers suggested that it might be due to higher levels and the role of iron in brain metabolism, which leads to reduced occurrence of febrile convulsion in those children. This study of course could simply assess the role of increasing iron in relation to febrile seizure and cannot be an appropriate scale to measure iron deficiency anemia and febrile convulsion. On the other hand low risk of febrile convulsion in the patients could be due to several other clinical condition that they may have.[10] On the other hand, some studies have reported findings that are not similar to the present study. for instance in Kobrinsky *et al.*'s study the febrile convulsion group suffered less from iron deficiency and it was concluded that iron deficiency could have a protective effect against febrile seizure.[11] In a study by Bidabadi , iron deficiency in febrile convulsion group (44%) was less than in the control group (48%), but since there was no significance difference , the protective effect of iron deficiency against febrile convulsion was not confirmed.[12] The possible explanation for these discrepancies are differences in age, nutritional habits, geographical area, sample size, general economic status and diagnostic criterion. Ferritin is an acute phase reactant and is non specific in any febrile disease.[13] this is confirmed by the higher plasma ferritin levels in the patient groups than in the healthy group. fever can cause the lack of difference in ferritin levels between two patient groups. in any case, use of plasma ferritin cannot simply be an efficient criterion for the diagnosis of iron deficiency in febrile children.

CONCLUSION

Our findings suggest that low serum iron levels and the presence of anemia can serve as strengthening factors for the Febrile seizures in children. Therefore, ID(Iron deficiency) can be added to the list of risk factors for febrile convulsions. Accordingly, children with FSs are suggested to be monitored for diagnosis and treatment of IDA. Furthermore, it is advisable to prescribe iron supplements earlier and more carefully to children who have important and well known risk factors for febrile convulsion, such as family history of febrile convulsion. It would be worthwhile to conduct a study to follow up children with ID, who are stricken by febrile convulsions after the treatment of ID, in terms of the recurrence rate of febrile convulsion.

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