Original Research Article

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Association of iron deficiency states and febrile seizures in children-a case control study

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ABSTRACT

Background: Iron deficiency being a potentially modifiable and treatable cause of febrile seizures. Objectives of Study was to identify Iron Deficient States or Anemia in children with febrile seizures as evidenced by low hemoglobin, altered RBC indices and altered Iron profile, and to determine the association of Iron deficiency states or anemia with febrile seizures.

Methods: This was a Case control study done between July 2013 to June 2014, on 50 indoor cases of febrile seizures in the age group of 6-60 months and 50 age and sex matched controls (fever without seizure) in department of Paediatrics, Hindu Hriday Samrat Balasaheb Thackeray Medical College (HBTMC) and Dr R.N. Cooper Hospital, Mumbai. Detailed clinical history and examination findings were noted. Cases and control were investigated with complete blood count, RBC indices, peripheral smear, S. Ferritin, S. Iron and TIBC. SPSS software package was used for statistical analysis. P<0.05 was considered as significant.

Results: 74% of cases and 66% of controls had low hemoglobin. MCV was low in 54% of cases and 34% of controls. RDW was raised in 46% of cases and 26% of controls. Iron deficiency anemia was prevalent among both cases and controls. Latent iron deficiency state suggested by low S. Iron and high TIBC in cases and control group was not significant in our study. However statistically significant lower Median S. Ferritin was noted in the febrile seizure group versus the controls (Cases-153.5, Control-173.0, p=0.0195) suggesting significant prevalence of prelatent iron deficiency state among cases.

Conclusions: Prelatent iron deficient state in children are more prone for febrile seizures.

Keywords: Anemia, Child, febrile, Convulsion, Iron deficiency

INTRODUCTION

Febrile seizures are a common occurrence in the paediatric population and a cause of great parental anxiety and concern. Greater concern is regarding the risk of recurrence of the same. The magnitude of the problem as evidenced by its high incidence of 3-4% in young children cannot be underestimated. Numerous studies have been performed worldwide investigating the

incidence, recurrence and risk factors associated with febrile seizures. While most studies have identified multiple non-modifiable risk factors such as family history, age of onset, type of seizures and temperature at presentation, few studies have evaluated factors which are modifiable. Iron deficiency affects at least a third of the world's population and is second only to hunger, as a major worldwide, nutritional problem. ¹ Iron deficiency anemia is a very well-known concept but what is often

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not appreciated is the broad canvas of effects of iron deficiency on various tissues, organs and systems in human beings in addition to iron deficiency anemia (IDA) leading to concept of "Iron deficiency disease". Anemia is just one manifestation of iron deficiency, there are other forms of mild to moderate iron deficiency in which anemia is absent, but tissue function is impaired.

Akman et al, in their study performed in Turkey, show that one does not have to be anemic from iron deficiency to demonstrate evidence of developmental deficits. Iron deficiency alone can do this.²

Further studies have shown that anemia is a poor predictor of iron deficiency among toddlers in Unites States.³ It was found that among toddlers, the positive predictive value of a haemoglobin concentration of under 11g/dl for the presence of iron deficiency is just 29%. Most iron deficiency, therefore, will be missed if one uses only haemoglobin as a screening technique to detect iron deficiency.

The importance of Iron for the functioning of a variety of critical enzymes essential for human survival such as catalase, aconitase, ribonucleotidereductase, peroxidase and cytochromes are a well-established and unquestionable fact. Neurocognitive defects due to Iron deficiency may be related to impaired neurotransmitter effects and defective myelination. Infants and toddlers, who are at a critical period of neurodevelopment, may be at particular risk for such effects. Iron deficiency has been found to be associated with lowering threshold for seizures, with fever potentiating this effect.

Studies have been performed in the recent past evaluating the relation between Iron deficiency and febrile seizures, however results have been conflicting and not altogether convincing. However, as consequences of Iron deficiency may occur in the absence of anemia, it is also important to study the Iron deficiency states by evaluating parameters like serum iron, total iron binding capacity and transferrin saturation.

Iron deficiency being a potentially modifiable and treatable cause, a positive association is of relevance in prevention and management and is reassuring for both the physician and parent.

METHODS

This study was case control study conducted on Indoor cases of febrile seizures and age and sex matched controls admitted in the paediatrics ward and intensive care unit of HBTMC and Dr R. N. Cooper hospital, Mumbai, over a period of 1 year, with case study proforma and consent which was previously reviewed and accepted by the hospital's ethics committee.

Objectives of study was to identify iron deficient states or anemia in children with febrile seizures as evidenced by low hemoglobin, altered RBC indices and altered iron profile, and to determine the association of iron deficiency states or anemia with febrile seizures.

Study duration

1yr (July 2013 to June 2014)

Sample size

All the admitted patients meeting inclusion criteria over a period of 1yr were included in study.

Study population

All children in the age group of 6 month-5 years, hospitalized fulfilling the inclusion criteria.

Inclusion criteria

Case is defined as child (Male/Female) in the age group of 6 months to 60 months, admitted for febrile seizures in the department of paediatrics. Control is defined as an age and sex matched child admitted with fever

Patient meeting inclusion criteria, whose parents /guardians were willing to give written informed consent.

Exclusion criteria

- CNS infections
- Seizure disorders
- Developmental delay and cerebral palsy
- Child on iron therapy
- Other anaemias-megaloblastic /haemolytic etc.

Study methodology

50 cases and 50 controls were enrolled based on the inclusion and exclusion criteria after taking informed consent.

Patients's clinical details and blood reports were entered in the case proforma. (Appendix I attached). Details of demography, clinical history including duration of fever, type of seizures, associated morbidities, and family history of febrile seizures/epilepsy were collected. General and systemic examination findings were noted.

Cases and control were investigated with complete blood count with RBC indices and peripheral smear, Serum Ferritin, Serum Iron and TIBC. Hemoglobin and RBC indices were measured by photometric measurement using ERMA Coulter PCE-210 (Japan) analyzer. Serum ferritin was measured by immunoturbidimetric assay method using the Roche/Hitachi Cobas C system. Serum Iron was measured by colorimetric method using the Roche/Hitachi Cobas C system. Transferrin saturation was calculated by the formula S. Iron/ TIBC x 100.

Febrile seizures: The International League Against Epilepsy (1993) defines a febrile seizure as "a seizure occurring in childhood between 1 month and 5 years of age, associated with a febrile illness not caused by an infection of the central nervous system infection, without previous neonatal seizures or a previous unprovoked seizure and not meeting criteria for other acute symptomatic seizures."

Simple/typical: Within 24hrs of onset of fever, brief<15mins, generalized, brief post ictal drowsiness, only once in 24 hrs.⁵

Complex/atypical: After 24hrs of onset of fever, prolonged>15mins, focal, multiple seizures/day.⁵

Iron deficiency states: Prelatent Iron deficiency: Tissue stores of Iron are depleted. Detected by low S. Ferritin levels.⁶

Latent iron deficiency: Reticuloendothelial stores are depleted. Erythropoeisis begins to be limited. Detected by decrease in S. Iron and increase in Total Iron Binding Capacity. Bulk of the erythrocyte population appears normal.

Frank iron deficiency anaemia: Iron deficiency has persisted long enough that a large proportion of circulating erythrocytes were produced after Iron became limiting. Detected by erythrocyte microcytosis and hypochromasia and low hemoglobin.

Reference values for age related normal haemoglobin, RBC indices and serum iron profile are attached as Appendix II.⁷

Iron deficiency, systemic and brain iron metabolism, the role of iron in the nervous system, and the neurologic manifestations of iron deficiency in childhood are reviewed.⁵

Statistical analysis

SPSS software package was used for statistical analysis. Baseline continuous variables were compared between groups using student 't' test. Odds ratio and confidence interval was used for comparison of data between matched cases and controls. P<0.05 was considered as significant.

RESULTS

Serum ferritin

Serum Ferritin level was low in 2% cases, normal in 8% cases and high in 90% cases. Comparing cases and controls using Students "t" test, it was found that low Ferritin was not significantly associated with occurrence of febrile seizures (p=0.276). The odds ratio was found to

be one which shows there is association between low Ferritin and occurrence of febrile seizures.

However, the median Ferritin in cases though higher than the normal range-153.5 was lower than in controls-173.0 which was statistically significant (p=0.0195) (Table 1).

Serum iron and TIBC (Total Iron Binding Capacity)

Only 12% of cases were found to have latent Iron deficiency as evidenced by low serum iron, while 28% of cases and 28% of controls had a high TIBC. Comparing cases and controls using Students "t" test, it was found that low Serum Iron was not significantly associated with occurrence of febrile seizures (p=0.832). Odds ratio is 6.68. Similarly, no significant difference was found between TIBC among cases and controls (p=0.721). The odds ratio was 0.81 which was statistically significant

The median Serum Iron among cases though within the normal range-128.6 mcg/dl was higher than that of controls- 128.2mcg/dl, which was statistically not significant. (p=0.182). Median TIBC among cases though in normal range- 368.5mcg/dl was higher compared to controls- 309mcg/dl however the difference was not found to be statistically significant (p=0.434) (Table 1). Frank Iron deficiency anemia as evidenced by low Hb was found in 74% of cases and 66% of controls.

RBC indices (hemoglobin, peripheral smear (PS), mean corpuscular volume (MCV), mean concentration of hemoglobin (MCH) and red cell distribution width (RDW)

In the present study 58% of cases and 50% of controls had PS evidence of Iron deficiency with no significant statistical difference. In the present study, 54% cases and 34% controls had a low MCV. In the present study,66% of cases and 54% of controls were found to have low MCH. 46% of cases and 26% of controls had a high RDW. By using Students "t" test, no significant difference in hemoglobin levels was found between cases and controls (p=0.915). The odds ratio was 1.46 which was not statistically significant. The median Hb of cases was 10.0g/dl which was lower than in controls- 10.4g/dl which was not statistically significant (p=0.774). By using Students "t" test, no significant difference in MCV levels was found between cases and controls (p=0.982). The odds ratio was 2.27 which was not statistically significant.

In the present study, 54% cases and 34% controls had a low MCV with median MCV among cases though lower than normal range-67.8flbeing much lower than in controls-71.9 with no statistical significance (p=0.714). In the present study,66% of cases and 54% of controls were found to have low MCH with the median MCH among cases though lower than normal range- 20.1 was much lower than that of the controls- 22.9, with no statistical significance (p=0.919).

Table 1: Association of iron deficiency states using hemoglobin, altered RBC indices and altered iron profile with febrile seizures.

Parameter	`S		Statistical	Analysis		
	Cases (n=50)	Controls(n=50)		Cases (n=50)	Control (n=50)	p value
Prelatent i	iron deficiency as	evidenced by low for	erritin levels			
Serum Ferr	ritin		Mean	149.6 <u>+</u> 175.6	170.0 <u>+</u> 176.3	0.276
Low	1 (2%)	0 (0%)	Median	153.5	173.0	0.0195
Normal	4 (8%)	2 (4%)	S.E. of Mean	12.42	12.46	
High	45 (90%)	48 (96%)	S.D.	87.82	88.16	
Latent iro	n deficiency as ev	idenced by low S. Iı	ron and TIBC	C		
Serum Iro	n		Mean	113.56 <u>+</u> 112.7	116.4 <u>+</u> 112.9	0.832
Low	6 (12%)	1 (2%)	Median	128.6	128.2	0.182
Normal	44 (88%)	49 (94%)	S.E. of Mean	8.67	7.99	
TIBC			Mean	370.8 <u>+</u> 204.5	351.4± 205.2	0.362
Low	9(18%)	12(24%)	Median	368.8	309.0	0.434
Normal	27(54%)	24(48%)	S.E. of Mean	14.46	14.37	
High	14(28%)	14(28%)	S.D.	102.25	102.6	
		ia as evidenced by			CH and RDW	
Hemoglob			Mean	9.89+ 3.28	10.16+ 3.49	0.441
Low	37 (74%)	33 (66%)	Median	10.0	10.4	0.774
Normal	13 (26%)	17 (34%)	S.E. of Mean	0.232	0.247	
			S.D.	1.64	1.747	
II) Iron de	eficiency in PS					
Present	29 (58%)	25 (50%)				
Absent	21 (42%)	25 (50%)				
III)MCV	,		Mean	68.52+ 19.76	72.41+ 21.66	0.067
Low	27 (54%)	17 (34%)	Median	67.80	71.9	0.714
Normal	23 (48%)	33 (66%)	S.E. of Mean	1.397	1.531	
			S.D.	9.878	10.832	
МСН			Mean	20.73± 8.32	22.32± 10.78	0.93
Low	33 (66%)	27 (54%)	Median	20.1	22.9	0.919
Normal	17 (34%)	23 (46%)	S.E. of Mean	0.588	0.762	
			S.D.	4.159	5.391	
RDW			Mean	14.70 <u>+</u> 2.91	14.17 <u>+</u> 4.94	0.231
High	23 (46%)	13 (26%)	Median	14.50	13.80	0.098
Normal	27 (59%)	37 (74%)	S.E. of Mean	0.205	0.349	
			S.D.	1.455	2.471	
Iron defici	iency as evidenced	l by low transferrin				
TSI	•	•	Mean	39.96+ 49.95	36.91 <u>+</u> 51.02	0.487
Low	21 (42%)	18 (36%)	Median	41.88	35.87	0.096
Normal	29 (58%)	32 (64%)	S.E. of Mean	3.497	3.607	
			S.D.	24.974	25.512	

By using Students "t" test, no significant difference in MCH levels was found between cases and controls

(p=0.625). The odds ratio was 1.65 which was not statistically significant. 46% of cases and 26% of controls

had a high RDW. The median RDW among cases was lower incases- 14.5 compared to controls -13.8 with no

statistical significance (p=0.098).

Table 2: Comparison of present study with previous studies.

Author, period	Diagno	stic criteria	for Iron	Deficiency					Conclusions
of study, Number studied, age group	Hb g/dl	MCV Fl	MCH Pg	RDW %	S.Ferritin ng/ml	S.Iron mcg/dl	TIBC mcg/dl	Conclusions	
Present study 2013-14 n=50 6m-60m	<5y: <11 5- 12y: <11	<2y: <70 2- 6y:<75	<5y: <23, 2- 6y:<24	>14.5	1-5y:6-24 6-9y:10-55	1- 5y:22- 136 6- 9y:39- 136	1- 5y:268- 441 6- 9y:240- 508	Significantly lower median S. Ferritin is noted in the cases.	Significantly lower median S. Ferritin is noted in the cases.
Pisacane et al ⁸ Jan 1993 to June 1995 n=156 6-24months	<10.5	<70	-	-	-	<5.4	-	Anemia was significantly more in cases (30%) than hospital (14%) and population (12%) controls	Anemia was significantly more in cases (30%) than hospital (14%) and population (12%) controls
Daoudet al ⁹ Jan-Dec 2000 n=75 3months-6yrs	<11	<70	<24	-	<30	-	-	Proportion of cases with plasma Ferritin<30micg/l was higher among cases. Hb, MCV, MCH were lower in cases, not statistically significant	Proportion of cases with plasma Ferritin<30micg/l was higher among cases. Hb, MCV, MCH were lower in cases, not statistically significant
Rehman et al ¹⁰ Jan-Dec 2001 n=30	<10	<70	<24	-	<10	-	-	Plasma Ferritin was significantly lower in cases as compared to controls	Plasma Ferritin was significantly lower in cases as compared to controls
Hartfield et al ¹¹ Jan2001- May 2006 n=361cases,390 controls 6months-3 yrs	<11	<70	-	>15.6	-	-	-	Cases were 1.83 times more likely to be iron deficient as compared with controls	Cases were 1.83 times more likely to be iron deficient as compared with controls
Vasvani et al ¹² Aug 2005- July 2006 n=50 6m-6yrs	<11	<70	<27	-	<12	-	-	Mean S. Ferritin was significantly lower in children with 1st febrile seizure	Mean S. Ferritin was significantly lower in children with 1 st febrile seizure
Leela kumari et al ¹³ Aug 2009- Feb 2010 n=154 6m-3yrs	<11	-	-	>15%	<12	-	-	All three Parameters were significantly different among cases and controls.	All three Parameters were significantly different among cases and controls.
Abdurrhaman et al ¹⁴ Jan 2006 – July 2009 n=112 5 m-4yrs	<10.5	<70	-	-	-	<22	>400	IDA more prevalent in cases compared to controls (p=0.003)	IDA more prevalent in cases compared to controls (p=0.003)
Susan et al ¹⁵ July 2007-June 2009, n=132 cases 88 controls 9m-5yrs	<10.5	<70		-	- <12	-	-	No significant difference in parameters between the 2 groups.	No significant difference in parameters between the 2 groups.
10 Mashouf et al ¹⁶ < 2SD for age March 2005- Sep 2006 n=200 6m-5yrs		<2y: <70 2-6y:<75		<5y:<23, 2- 6y:<24	- <7	<1y:<40 >1y: <50	<1y:<40 >1y: <50	The amount of RBC, serum Iron, and plasma Ferritin were significantly higher, and TIBC was significantly lower amongthe cases	

By using Students "t" test, no significant difference in RDW levels was found between cases and controls (p=0.231).

The odds ratio was 2.42 which was not statistically significant (Table 1).

Transferrin saturation index (TSI)

Comparing cases and controls using Students "t" test, it was found that low TSI was not significantly associated with occurrence of febrile seizures (p=0.487).

The odds ratio was found to be 1.28 which was not significant. 42% of cases and 36% of controls had a low TSI. The median TSI among cases was lower in cases-41.88 compared to controls-35.87 and the difference was not statistically significant (p=0.096) (Table 1).

DISCUSSION

When the Iron Deficiency States were studied in the present study, prelatent iron deficiency suggested by significantly lower level of median Serum Ferritin was found in the cases compared to the controls (Cases-153.5, control-173.0, p=0.0195). Such an observation has been reported in earlier studies (Table 2).

Latent Iron deficiency state suggested by low Serum Iron and High TIBC in cases and control group was found not significant in our study.

Low Serum Iron among cases was found in few studies and lower level of Serum Ferritin among cases was found in other studies. 8-10,12,13 Transferrin Saturation Index has not been studied in previous studies (Table 2).

In the present study, Frank Iron Deficiency anemia as evidenced by low Hemoglobin and microcytosis was common in both cases and controls. There was no statistically significant difference between the 2 groups. However, few studies have shown IDA to be more prevalent among cases compared to controls.^{8,11,13} (Table 2). It is noted that the results of the various studies are inconsistent and not very convincing. Iron Deficiency, though simple to treat, does not have a reliable parameter that reflects the deficiency state.

We can rely upon simple parameters like low MCV, MCH and raised RDW as indicators of iron deficiency.

Iron deficiency being a potentially treatable risk factor, further studies with larger sample size would be of interest and help to validate the association of the iron deficiency states with febrile seizures.

CONCLUSION

In this case control study conducted from July 2013 to June 2014, 50 cases of febrile seizures admitted in the

Department of Paediatrics were studied. 50 age and sex matched controls were selected.

It is noted that iron deficiency anemia is prevalent among both cases and controls. Latent Iron deficiency state suggested by low Serum Iron and High TIBC in cases and control group was found not significant in our study. However statistically significant lower Median Serum Ferritin was noted in the febrile seizure group versus the controls (cases-153.5, Control-173.0, p=0.0195).

It is hereby concluded that both the groups had a high prevalence of iron deficiency anemia with statistically significant lower Median Serum Ferritin among children with febrile seizures proving the hypothesis that prelatent iron deficient state in children are more prone for febrile seizures. Due to high prevalence of manifest iron deficiency anemia among peadiatric age group this study is unable to show direct correlation between frank iron deficiency state and latent iron deficiency state with febrile seizures.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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Unit:

Appendix I

Study Proforma

Subject no./Name:

DOB/age:				Sex:				
Hospital no.:				In pa	atient no.:			
DOA:				DOI	D:			
Diagnosis:								
Presenting comp	olaints:							
1.Fever:		emperature			Duration:			
2.Seizure:	Fi		Recurrence		Typical		Atypica	1
Description:			110001101100		Тургош		110) p100	-
Duration:								
Post ictal								
Recurrence	Δ	ge of onset			Nature of 1s	st seizure		
Other complaint		ge of offset			rature or r	SCIZUIC		
RS		VS	GIT		CNS		Renal	
Birth history:	C	V 5	OH		CIAD		Kenai	
Developmental 1	history	Λ.	opropriate			Dolov		
		A	эргоргіасе			Delay		
Immunisation hi	istory:	D-1-4: 4-	11	T-1	:1:		F-:1	-
Family history:	- 4 *	Relation to	tne patient	Febr	rile seizures		Epileps	У
General examina	ation:	*** * 1 .		TIG.			4.5	
Height:	***	Weight:	`	HC:		0.00	AF:	
Temp:	HR:	R		BP:		GCS:	Spo2	
`	_	ue sclera/platy/ko	ilonychia:					
Focus of infection								
Signs of vitamin	deficien	icy:						
Neurocutaneous		:						
Dysmorphic fea	tures:							
Skull and spine:				Func	dus:			
Systemic exami	nation:							
CNS:								
CVS:								
RS:								
PA:								
							Profo	rma cont
Investigations:								
	Hb	m 11 /	D1. 11./	ESR	Maria	MCH	MCHC	RDW
Date:	g/dl	Tc cells/cmm	Plt cells/cmm	mm/hr	MCV fl	pg	g/dl	%
Peripheral smea						r &	<u> </u>	
RBCS:								
WBCS:	N	L		В	M	Е		Bands
Platelets:		<u>E</u>			171			Durius
Serum iron prof	ile.							
Date:	110.	S. Ferritin ng	r/m1	C	Iron ug/dl		Tibc ug/dl	
CSF analysis:		S. Perruii iig	3/1111	ა.	non ug/ui		Tibe ug/ui	
	C-11 4	- C-11	C1	D.,	-4-: C	1-1 1-1 -	C Ctain	C14
Date	Cell typ	e Cell count	Glucose	Pr	otein C	hloride	G. Stain	Culture
Others:								
EEG:								
Neuroimaging:								
Urine routine:				Ur	rine culture:			
Blood culture:								
RBS:		NA:		K:			Urea:	
Creat:		AST:		Al				
CRP:				CX	XR:			

Control 1

Hospita	al no.:			IP no.:				
Date:	Hb g/dl	Tc cells/cmm	Plt cells/cmm	ESR mm/hr	MCV fl	MCH pg	MCHC g/dl	RDW %
Periphe	ral smear:							
RBCS:								
WBCS:	N	L		В	M	Е		
Platelet	s:							
Serum i	ron profile							
Date:		S. Ferritin ng/1	ml	S.	Iron ug/dl		Tibc ug/dl	

Appendix II

Reference values age related normal haemoglobin values⁵⁰

Age	Hemoglobin (g/dl)	
2mnths-2yrs	9.0-14.0	
2-12yrs	11.5-15.5	

Age related normal values of RBC indices 50

MCV (fl)		
Age	Mean	-2SD
0.5 to 2 years	78 <u>+</u> 8	70
2 to 6 years	81 <u>+</u> 6	75
MCH (pg)		
Age	Mean	-2SD
0.5 to 2 years	27 <u>+</u> 4	23
2 to 6 years	27 <u>+</u> 3	24
MCHC (g/dl)		
Age	Mean	-2SD
0.5 to 2 years	33 <u>+</u> 3	30
2 to 18 years	34 <u>+</u> 3	31
RDW (%)		
Red cell distribution width	All ages	11.5%-14.5%

Age related normal values for serum iron profile⁴

Serum ferritin: (ng/ml)		
Age	Male	Female
7-12 months	6-80	6-45
1-5 years	6-24	6-24
6-9 years	10-55	10-55
Serum iron: (mcg/dl)		
Age	Male	Female
1-5 years	22-136	22-136
6-9 years	39-136	39-136
TIBC (mcg/dl)		
Age	Male	Female
1-5 years	268-441	268-441
6-9 years	240-508	240-508