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Is there a need for routine screening and treatment of iron deficiency anemia in early childhood to decrease incidence of febrile seizures?

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ABSTRACT:-

Background: The aim of our study was look for association between iron deficiency anemia with febrile seizures. Prior to our study several other studies have given a conflicting data regarding this association and therefore it was high time for us to confirm this association

Methods: This was a hospital based case-control study which was conducted over a period of 1 year. We enrolled 50 cases and 50 controls. Cases included patients who had a seizure episode following febrile illness. Control group comprised of children of same age group with a febrile illness but without a seizure.Parameters which were determined in each sample of study group; Hb, MCV, MCH, MCHC, Serum Iron, Serum Ferritin, Transferrin saturation, TIBC. The data collected was analyzed and Scrutinized by Statistical package for social sciences (spss) and Minitab 11.30. Chi-square test and student-t test were applied to draw the inferences.

Results: By applying logistic regression, we saw odds ratio of 1.064(C.I 1.032-1.097) for iron deficiency patients to have febrile seizures ($p<0.0001$).

Conclusion: The results of our study suggest that IDA is a risk factor for febrile seizures and screening for IDA should be considered. Early detection and timely correction of iron deficiency may be helpful for prevention of simple febrile seizures in children of this age group.

Introduction:

Seizures are common in pediatric age group and occur in approximately 10% of children[1,2]. Seizures are a common neurological symptom in sick children and are common causes of pediatric admission to hospitals[3,4]. In children they include febrile seizures, acute symptomatic seizures (e.g.in a child pyogenic meningitis) and seizures in a child with epilepsy[3,4,5,6]. Febrile seizures are the most common type of seizures in infants and small children and are triggered by fever occurring in 2-5% of children[2,7]. A febrile seizure is defined as a seizure occurring during fever with rectal temperature of at least 38.3^0c or an axillary temperature of at least 37.8^0c during fever, between the ages 6 months to 5 years in absence of intracranial infection or history of a previous unprovoked seizure.[3,4,6,8]. Febrile seizures are age dependent and are rare before the age of 9 months and after 5 years of age, with peak incidence at approximately 18 months of age[9,10,11]. Average age of febrile seizures has been found to be 23.3 months by Nelson and Ellenberger. Studies have shown that the period of most rapid postnatal hippocampal growth is between birth and 24-36 months which closely corresponds with the time period during which almost infants and children are susceptible to febrile seizures, 95% of cases occurring before 36 months[12,13]. Febrile seizures result from a combination of both environmental and genetic factors.[2,4,14,15]. 24% of those who have

febrile seizure have a positive family history of seizures with 4% having family history of epilepsy[4,16,17]. Linkage studies in several large families have mapped the gene to chromosome 19p and 8q13-21. An autosomal dominant inheritance pattern has demonstrated in some families [2,4,9,18,19]. Iron is a nutritional element not only needed for the synthesis of hemoglobin, but is also essential for enzymes involved in neurochemical reactions. Neurological symptoms like poor attention span, learning deficits, weak memory, delayed motor development and behavioral disturbances caused by iron deficiency are well known[20,21,22].

Iron is important for normal neurological functions like Neurotransmitter metabolism[23], Myelin formation[24] & Brain energy metabolism[25,26,27,28].

Further the fact the fever can worsen the negative effects of low serum ferritin on brain and trigger a seizure, provides a clue towards the role of iron deficiency anemia in the causation of febrile seizures. Thus it is possible that iron deficiency may predispose to other neurological disturbances like febrile seizures. Age for peak incidence of febrile seizures is 14 to 18 months which overlaps with that of iron deficiency anemia which is from 6 to 24 months[29,30].

Methods:

The study was a hospital based case-control study which was conducted in the department of pediatrics at a tertiary care teaching hospital in North India. The study was conducted over a period of 1 year. We enrolled 50 cases and 50 controls in this study. Cases were defined as those patients in age group of 6 months to 5 years who had a seizure episode following febrile illness, in absence of a CNS infection. Control group comprised of children of same age group with a febrile illness but without a seizure following febrile illness in them. Controls were group matched to cases on age and sex.

On an average around 335-470 cases of febrile convulsions are admitted in our hospital annually. 15% of expected admission of febrile convulsions was taken as the sample size for cases. Keeping this in view and by applying power of 95% and alpha error of 0.05 and sample proportion of 1:1 for cases and controls, 50 cases and 50 controls were enrolled in this study.

Exclusion criteria:

A) Children with metabolic diseases

B) Children with connective tissue disorders

C) Children with CNS diseases and infections or congenital or acquired abnormalities of CNS.

D) Children with genetic abnormalities with known risk for seizure.

E) Children with known history of seizure disorder.

F) Thallasemia

Inclusion criteria:

A) All children of age group 6 months to 5 years with febrile illness with otherwise healthy

B) Fever more than 38.4 degree Celsius

C) In a child experiencing febrile seizures, one of the below listed seizure manifestations were experienced

- Twitching and jerking of face and extremities.
- Up rolling of eyeballs.
- Stiff body
- Unconsciousness
- Inability to talk
- Problems with breathing
- Involuntary urination and/or defecation.
- Frothing from mouth

Seizure details, focus of febrile illness, family history of epilepsy/febrile seizures were recorded for all cases and controls.

Parameters which were determined in each sample of study group; Hb, MCV, MCH, MCHC, Serum Iron, Serum Ferritin, Transferrin saturation, TIBC.

Iron deficiency anemia was defined as: Hemoglobin <11g/dl, MCV <70fl, MCH <27pg, MCHC <30gm Hb/dl RBC, Plasma ferritin <12 mcg/l, Serum iron < 40mg/dl, Transferrin saturation < 16%, TIBC >430mcg/dl. In presence of fever, a higher cut-off value of plasma ferritin (25-50mcg/l) was considered. The data collected was analyzed and Scrutinized by Statistical package for social sciences (SPSS) and Minitab 11.30. Chi-square test and student-t test were applied to draw the inferences.

Results:

Table 1: Age & Sex distribution of patients with febrile seizures.

Age (Year)	Male	Female	Total
6 Mon-1yr	5	4	**9**
1-2	19	12	**31**
2-3	3	2	**5**
3-4	2	1	**3**
4-5	2	0	**2**
Total	**31(62%)**	**19 (38%)**	**50**

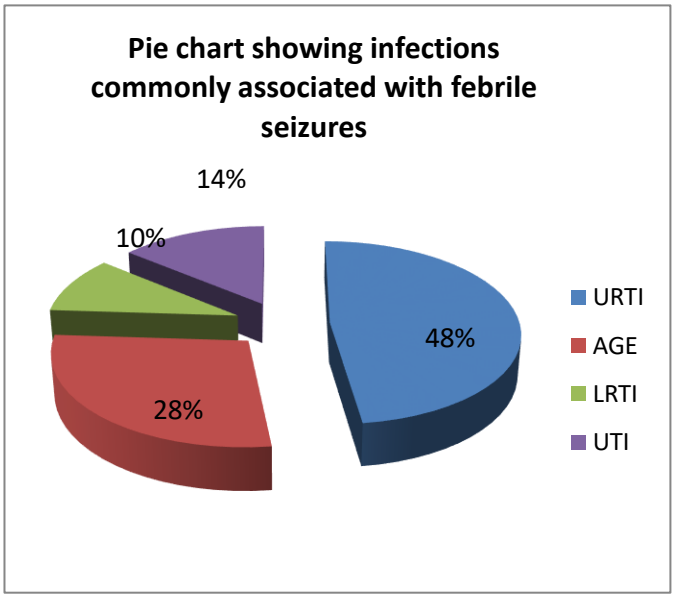
Table 2: Age and type of febrile seizures.

Age (Year)	Typical	Atypical	Total
6 Mon-1yr	8 (88.8%)	1 (11.2%)	**9**
1-2	26 (83.8%)	5 (16.2%)	**31**
2-3	4 (80%)	1 (20%)	**5**
3-4	2 (66.6%)	1 (33.4%)	**3**
4-5	1 (50%)	1 (50%)	**2**
Total	**41 (82%)**	**9 (18%)**	**50**

The above table and graph show that typical febrile seizure was more common than atypical febrile seizure in the age group of 1-3 years (83.3% vs 16.7%).

The above table and graph also show that typical febrile seizure was more common in overall age group as compared to atypical febrile seizure (82% vs 18%)

Fig. 1: Common focus of infections associated with febrile seizures.



The above pie chart shows that URTI was the most common infection which was associated with febrile seizure followed by acute gastroenteritis.

Table 3: Relationship of peak temperature with febrile seizure.

	Cases	Controls
Mean Temp. (^{0}C)	**38.82**	**38.59**
Standard Deviation	**0.60**	**0.45**
95% Confidence Interval	**38.65-39.01**	**38.46-38.72**
P –value	**0.03**	

The above table shows that peak temperature among children with febrile seizure was 38.82^{0}C which was higher than 38.57 ^{0}C seen in control group. This relationship was statistically significant with p value of 0.03.

***Table 4: Comparison Of Various Indices Of Iron Status In Cases And Controls*:**

Variable	HB		MCV		MCH		MCHC		SERUM FERRITIN		SERUM IRON		TRANSFERRIN SATURATION		TIBC	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
MEAN	10.78	11.47	70.32	75.29	23.992	25.522	30.946	31.83	38.142	43.330	74.08	88.28	29.50	34.94	312.96	290.70
MEDIAN	10.9	11.6	70.50	75.80	23.900	25.650	30.000	31.350	37.950	42.500	73.00	90.00	28.00	36.00	320.50	287.50
STANDARD DEVIATION	.977	.955	3.849	3.74	1.49	1.71	2.036	1.734	4.436	5.036	13.065	15.353	5.448	6.484	32.660	26.223
95% CONFIDENCE INTERVALS	10.504-11.059	11.204-111.747	69.229-71.418	74.225-76.354	23.566-24.418	25.034-26.010	30.367-31.504	31.337-32.322	36.881-39.402	41.898-44.761	70.37-77.79	83.92-92.64	27.95-31.05	33.10-36.78	303.68-322.24	283.25-298.15
P VALUE	<0.0001		<0.0001		<0.0001		0.022		<0.0001		<0.0001		<0.0001		<0.0001	

Table 5: Impact Of Iron Deficiency On Febrile Seizures On Logiostic Regression Scale

	ODDS RATIO	**95% C.I**	**P-VALUE**
SERUM IROM	**1.064**	**1.032-1.097**	**<0.0001**

The above table shows that with odds ratio of 1.064(C.I 1.032-1.097) by applying logistic regression that there is strong association between iron deficiency and febrile seizures (p<0.0001).

Discussion:

Seizures are common in pediatric age group and occur in about 3-5% of children. Among the pediatric seizures, febrile seizures comprise the bulk of seizures.

Various risk factors have been found to with associated with febrile seizures. But till now no definite factor has been found.

This study was conducted to see whether there exists any association between iron deficiency anemia and febrile seizures. This study was conducted in the post-graduate department of Pediatrics in a tertiary care teaching hospital of north India over a period of one year. 50 children (including infants) with age between 6 months to 5 years who had presented with febrile seizure were included in the study group. An age and sex matched control group was chosen from children presenting with febrile illness but without seizures.

Our study showed that most common age group for the occurrence of febrile seizures was 1-2 yrs. It was also seen that incidence of febrile seizures was more in males (62%) than in females (38%). These findings are consistent with the previous studies by Bidabadi et. al[31]. Wei et al[15] had also obtained similar results. The higher incidence of febrile convulsions in males compared to females has also been found in Chinese, Malay and other parts of world[15]. Febrile seizures were most commonly seen in the children aged between 1-2 years with a mean age of 20.42 months. Similar results were observed by Aicardi et al[33,] and Stafstorm et al[34] in their studies. Higher incidence of febrile illness in this age group may be the cause for most of the febrile seizures occurring in this age group.

Our study revealed that typical febrile seizures were more common than atypical febrile seizures in all children between 6 months & 5 years of age (82% vs 18%). This finding is consistent with the study done by Bidabadi et al[31], in whose study simple febrile seizures had occurred in 66% of total patients as against 34% having of complex seizures. Similar results were also obtained by Tahir et al[10].

The study showed that mean peak temperature in patients with febrile seizure was 38.82^0C which was higher than mean peak temperature of 38.6^0C in controls (p=0.03).This finding was consistent with the studies done by Bidabadi et al[31], Berg et al[35].

Out of 50 cases 12 had a family history of seizures, as compared to only 4 patients in the control group (*p= 0.03*). This higher incidence of febrile seizure in patients with positive family history of seizures suggests that genetic factors play an important role in susceptibility to febrile convulsion as is shown by linkage analysis studies. Linkage studies have identified chromosomal loci for febrile seizures-FEB1 at 8q, FEB2 at 19p, FEB3 at 2q, FEB4 at 5q and FEB5 at 6q[34]. This finding has been confirmed by other studies like Abu-khalil et al[36], Hirose et al[37], Kugler et al[38] and Bidabadi et al[31].

In our study mean Hb(g/dl) in cases was 10.78 ±0.977g/dl as against 11.47±0.955g/dl in control (p value <0.0001). Mean MCV in cases was 70.32±3.849fl as against 75.29±3.74fl in control group (p value <0.0001). Mean MCHC in cases was 30.946±2.036g/dl compared to 31.83±1.734 g/dl in controls (p value 0.02). Mean MCH in cases in our study was 23.992±1.49pg as against 25.522±1.716pg in control group (p value <0.0001). Thus it is seen that Hb , MCV, MCH, MCHC were significantly low in cases compared to control group. These findings were consistent with the results which were observed by Naveed-ur-Rehman et al[39] in his study, thus pointing towards the role of iron deficiency in febrile seizures.

Comparing the iron profile indices of our study between cases and controls we found that mean serum ferritin level in case group was 38.142±4.436µg/dl as compared to 43.330±5.036µg/dl in control group(p value <0.0001). Mean serum iron level in the case group was also significantly lower than the control group (p value <0.0001). Similar pattern was seen for mean transferrin saturation, with a mean of 29.50±5.448 in cases compared to 34.94±6.484 in control group (p value< 0.0001). The total iron binding capacity in cases was 312.96±32.660µg/dl which was also significantly higher than control group 290±26.223µg/dl (p value <0.0001). The results of our study were consistent with previous studies. On logistic regression, a strong association was seen between iron deficiency and febrile seizures (*p*<0.0001, odds ratio 1.064).

Iron deficiency was found as a significant risk factor for simple febrile seizures in children of age

group 6 months to 5 years in our study. In a study by Pisacane, *et al*[40], similar results were noted with, an odds ratio of 3.3 (95% CI of 1.7-6.5). Iron status was measured by hemoglobin, MCV and serum iron in that study. Daoud, *et al*[41] also found similar results in children with febrile seizures. They found cases almost twice likely to have iron deficiency compared to controls. In the study done by Daoud, *et al*[41], significance of iron status as a possible risk factor was evaluated. The mean serum ferritin level in the cases (29.5 mcg/l) was much lower than in the controls (53.5 mcg/l). Similar observations were made in a study done by Vaswani, *et al*[42]. The mean serum ferritin level was significantly low in children with first febrile seizures (31.9±31.0 µg/dl) as compared to controls (53.9±56.5 µg/dl) (*P*=0.003). However, no significant difference was noted in the mean hemoglobin value of cases (9.4±1.2 g/dl) and controls (9.5±1.0 g/dl) (*P*=0.7), or in the mean value of blood indices. In our study, iron deficiency was diagnosed by taking into consideration the criteria *i.e.* hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, serum ferritin, serum iron, transferrin saturation, total iron binding capacity and all the parameters were significantly different among cases and controls.

The strength of our study included standardized criteria for diagnosing febrile seizures, and iron deficiency, elimination of incidence prevalence bias, concurrent enrolment of controls and cases, and no recall bias regarding exposure.

Serum ferritin, a nonspecific acute phase reactant can rise in any inflammatory conditions, but both cases and controls were having fever at the time of enrolment and thus it was not a confounding factor.

The limitation of our study is that Iron deficiency and lead poisoning may be associated and lead poisoning results in neurological manifestations. Blood lead levels could not be determined in our subjects.

Conclusion:

The results of our study suggest that IDA may be a risk factor for febrile seizures and screening for IDA in these patients should be considered. . Early detection and timely correction of iron deficiency may be helpful for prevention of simple febrile seizures in children of this age group.

Bibliography:

[1] Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia (1994), 35 Suppl 2: S 1-6.

[2] Johnston MV. Seizures in childhood. In: kleigman r.m., behrman r.e., jenson h.b., stanton b.p. Nelson text book of pediatrics 18th edition philadelphia: saunders elsevier, p. 2457-2470.

[3] Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. N engl med j 1976;295:1029-1033.

[4] Sadier LG, Scheffer IE. Febrile seizure. BMJ :2007,334:307-311.

[5] Huang CC, Chang YC, Wang ST. Acute symptomatic seizure disorder in children: A population study in southern Taiwan. Epilepsia 1998;39:960-996.

[6] Vragesh Udani, Neeta Naik, Nitin Shah, Deepak Ugra. Acute symptomatic seizures. Ch in IAP National guidelines , Unicef; 51 :2006.

[7] Alexander KC, Leung W, Lane M Robson. Febrile seizures. Epilepsia (2007) 21: 250-255.

[8] Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. Medical history and intellectual ability at 5 yrs of age. British med j 1985;290:1307-1315.

[9] Lynette G Sadleir, Ingrid E Scheffer. Febrile seizure BMJ 2007 Feb:10;334(7588):307-311.

[10] Tahir Saeed Siddiqui. Febrile convulsion in children. Relationship of family history to type of convulsion and age of presentation. Pakistan Pediatric J 2004 xii (2),73-81.

[11] Takayuki Tsuboi: Epidemiology of febrile and afebrile seizures in children in Japan. American Academy of Neurology 1984:34-175.

[12] Maytal J, Shinnar S. Febrile seizures. Paediatrics 1990;86:611

[13] Van Landindham KE, Heinz ER, Cavazos JE, et al. MRI evidence of hippocampal injury following prolonged focal febrile convulsions. Ann neurol 1998;43:413.

[14] Verity CM, Greenwood R, Golding J. Longterm individual and behavioral outcome of children with febrile seizure. N Engl J med 1998, 338:1723-1728.

[15] Wei Lung Lee, Poh Sim , Belinda, Uma Rajan. Epidemiology of febrile seizures in Singapore children . Neurol J Southeast Asia 1996;1:53-55.

[16] Luders H, Acharya J, Baumgartner C et al. Semiological classification of seizures. Epilepsia. Sep 1998 ;39(9):1006-1013.

[17] Offringa M, Bossuyt PM, Lubsen J, Ellenberg JH, Nelson KB, Knudsen FU et al. Risk factors for seizure recurrence in children with febrile seizures;A pooled analysis of individual patient data from five studies. J Pediatr 1994:124:574-584.

[18] Kjeldsen MJ, Kyvik KO, Friis ML, Christensen K. Genetic and environmental factors in febrile seizures; a Danish population based twin study. Epilepsy Res 2002;51:167-170.

[19] Verburg ME, Bruijnzeels, J.C Vander wooden et al. Incidence of febrile seizure in Neitherland: Neuro epidemiology 1992;11:169-172.

[20] Ambruso DR, Hays T. Goldenberg NA. Iron deficiency anemia. Current diagnosis and treatment-pediatrics. 19th edition. Denver usa:mcgraw hill, p. 810-11, 2009.

[21] Idirandinata P, Pollit E. Reversal of developmental delay in iron deficient infants treated with iron. Lancet 1993,341;1-4.

[22] Lozoff B, Brittenham GM. Behavioural aspects of iron deficiency. Prog Hematol 1986;14:23-53.

[23] Youdim MBH, Ben Shachar D, Yehuda S. Putative biological mechanism of effect of iron deficiency on brain biochemistry and behaviour.Am J Clin Nutr 1989;50:607-617

[24] Larkin EC, Rao GA. Importance of fetal and neonatal iron. Adequacy of normal development of CNS. In Dobbing J, editors.Brain Behaviour and iron.

[25] Erikson KM, Jones BC, Hers EJ, Zhang Q, Beard JL. Iron deficiency decreases D1 and D2 receptors in rat brain. Pharmacol Biochemical Behav 2001;69:409-418.

[26] Kwik-Uribe CL, Golub MS, Keen CL. Behavioral Consequences of Marginal Iron deficiency during Development in a Murine Model- Behavioral and physiological consequences. Neurotoxicol Teratol.1999;21(6);661-672.

[27] Pinero DJ, Li DQ, Connor JR, Beard JL. Variation in dietry iron alter brain iron metabolism in developing rats. J. Nutr 2000;130:254-263.

[28] Ramos A, Mormedi P. Stress and emotionality. A multidimensional and genetic approach. Neurosci Biobeha Rev 1998;22(1);33-57.

[29] Offringa M, Kroes AC, Derksen-Lubsen G. Viral infection in febrile seizure. J. Pediatr 1995:127;95-97.

[30] Chamberlain JM, Gorman RL. Occult bacteremia in children with simple febrile seizures. Dis Mon 2003;49:42678.

[31] Bidabadi E, Mashouf M. Association between iron deficiency anemia and ist febrile seizure: a case-control study. Seizure. 2009;48(5):347-351.

[32] Wallace RH, Berkovic SF, Howell, RA Sutherland GR, Mulley JC:Suggestion of a major gene for familial febrile convulsion mapping to 8p 13-21. J Med Genet 1996:33;308-312.

[33] Aicardi J. Febrile convulsion. Epilepsy in children.New York: Raven Press;1994, p253-275.

[34] Stafstorm C. The incidence and prevalence of factors in seizure.febrile seizure.academic press;2002:p1-25.

[35] Berg Anne T, S. Shinnar. Unprovoked seizures in children with febrile seizures. Neurology 1996 ;4:562-568.

[36] Abou-khalil B, Keri L, Lazenby B, Harris PA, Haines JL, Hedera P. Familial genetic predisposition, epilepsy localisation and antecedent febrile seizure, epilepsy res 2007;73(jan104-110).

[37] Hirose S, Mohney RP, Okada M, Kaneko S. the genetics of febrile seizures and related epilepsy syndrome brain dev .2003;25 (aug304-312).

[38] Kugler S,Johnson W. Genetics of febrile seizure susceptibility trait. Brain dev 1998,20(aug 265-274).

[39] Naveed-ur-rehman, Billoo AG. Association between iron deficiency anemia and febrile seizures. J coll physicians surg pak. 2005 jun;15(6):338-340

[40] Piscane A, Sanson R, Impaglizzo N. Iron deficiency anemia and febrile seizure. BMJ 1996;313(7153):343.

[41] Daud AS, Batieha A, Ekteish A, Gharaibeh N, Ajlouni S, Hijazi S. Iron status: a possible risk factor for first febrile seizures. Epilepsia. 2002;43:740-3

[42] Rajwanti KV, Praveen GD, Swati K, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. Indian Pediatr. 2010;47:437-9.