

## The Correlation of Iron Status and First Febrile Seizure: A Prospective Case-Control Study

Dr Jeetam Singh Meena,<sup>1</sup> Dr Sunita Meena,<sup>2</sup> Dr S. Sitaraman<sup>3</sup>

<sup>1</sup>Assistant Professor, Department of Paediatrics Medicine, SMS Medical College, Jaipur Rajasthan India

<sup>2</sup>Assistant Professor, Department of Anaesthesia, SMS Medical College, Jaipur Rajasthan India

<sup>3</sup>Professor and Head Department of Paediatrics Medicine, SMS Medical College, Jaipur Rajasthan India

### Abstract

**Background** Febrile seizures (FS) are the most common type of seizures in children and iron deficiency anaemia is most common type of anaemia in children. The relationship between iron deficiency anaemia (IDA) and first FS has been examined in several studies with conflicting results.

**Patients and Methods** In this prospective case-control study we assessed 84 children with a diagnosis of first FS, aged between 6 months and 5 years who were admitted in department of paediatrics of SPMCHI, SMS Medical College Jaipur Rajasthan, during August 2006 to Oct. 2007. The control group assessed 85 febrile children without convulsion; cases and controls were matched by gender and age. Patients and controls were reviewed to determine iron status using the haemoglobin concentration Hb, MCV, MCHC, MCH, S. iron, and TIBC, S. ferritin.

**Results** cases and controls were  $2.07 \pm 1.24$  and  $2.17 \pm 1.30$  ( $P > 0.05$ ) years of mean age, respectively. The Hb, MCV, MCH, MCHC and serum iron, and plasma ferritin were significantly lower among the cases with first febrile convulsions than in the controls and differences were statistically significant. The mean value in study group were significantly lower than Control group for Hb ( $9.39 \pm 1.75$  vs  $11.23 \pm 1.49$ ) ( $P < 0.0001$ ), MCV ( $70.47 \pm 7.91$  vs  $81.41 \pm 7.75$ ) ( $P < 0.0001$ ), MCH ( $22.26 \pm 3.70$  vs  $26.61 \pm 2.65$ ) ( $P < 0.0001$ ), MCHC ( $31.15 \pm 3.23$  vs  $32.92 \pm 2.0$ ) ( $P < 0.0001$ ), Ferritin  $< 20$  ng/dl ( $11.77 \pm 2.91$  vs  $5.200 \pm 0$ ) ( $P < 0.01$ ), S. Iron ( $33.90 \pm 18.07$  vs  $43.36 \pm 12.94$ ) ( $P < 0.0001$ ) respectively.

**Conclusion** IDA was significantly more frequent among children who had FS than those with febrile illness alone. The results suggest that IDA may be a risk factor for FS and screening and correction for IDA should be considered in children presenting with the first FS.

**Keywords:** -Iron status, Febrile seizure

### I. Introduction

Febrile convulsions are the most common form of childhood seizures<sup>1</sup>. Its incidence is about 2–5% in USA and Western Europe. In Japan approximately 6–9% of infants and children experienced at least one febrile seizure by age of 5 years, elsewhere varies from 5–10% and rates as high as 14% have been reported from the Mariana Islands in Guam<sup>17</sup>.

Although children with simple febrile seizure are at no greater risk of later epilepsy than general population, some factor associated with increased risk including atypical feature of seizure or febrile seizure before 9 months of age, delay development or a pre-existing neurological disorder<sup>1</sup>. Exact cause of simple febrile seizure is unknown but there is association between febrile seizure and epilepsy later in life,<sup>6</sup> therefore it's important to identify risk factor for febrile seizure, independent risk factors for febrile convulsions were height of temperature<sup>8</sup>, history of febrile convulsions in a first or in a higher degree relative<sup>7</sup>, maternal smoking and alcohol consumption during pregnancy, and perinatal exposure to antiretroviral<sup>9</sup>. Genetic factors contribute significantly to the etiology of febrile convulsion.

There were few studies shown association between iron deficiency anaemia and febrile seizure<sup>2,3,4,5</sup>. Iron deficiency anaemia is common disorder worldwide and in India its prevalence is about 50% in under five years of age<sup>10</sup>. Iron deficiency anaemia not a simple fall in Hb level, its affecting several system of body including central Nervous system<sup>15</sup>. Iron involved in synthesis of dopamine serotonin and GABA and myelin formation as well as in metabolism of several other neurotransmitters in brain<sup>11,12,13</sup>. There were few studies<sup>2,3,4,5,16</sup> published worldwide shown that iron deficiency increase risk of febrile seizure<sup>3,4,5,6</sup> while other<sup>15</sup> shown that iron deficiency protect from febrile seizure. In view of conflicting results of these studies, we planned present study which purpose was to assess the relation, if any, of iron status with first febrile Convulsion.

### II. Materials And Methods

The study group included all children with a diagnosis of first febrile convulsion (FFC), aged between 6 months and 5 years, without history of low birth weight at birth, previous convulsion, developmental

delay, neurological deficit, or CNS infection, neuromuscular disorder and without clinical evidence of malnutrition, hepatic disorder, renal disorder. Patients were treated at department of paediatrics of sirpadampt mother and child health institute, Jaipur SMS Medical College during august 2006 to Oct 2007. The control group was included febrile children at time of admission due to UTI, ARI, mild GI infection without convulsion or previous history of convulsion.

All cases and controls were with normal growth. Demographic information collected for cases and controls included age, and gender. Age (in months and years) was calculated from the date of birth. Information on birth weight and current weight, developmental milestones, body temperature on admission, cause of fever, history of iron supplement therapy, family history of febrile convulsion and epilepsy were recorded for all cases and controls, as well as details of the seizure history, duration, frequency, type of seizure (simple or complex), and duration between initiation of fever and convulsion for cases with FFC. A single seizure of <15 min duration in the presence of fever without focal features was defined as a simple febrile convulsion, whereas seizures were defined as complex if they lasted >15 min, had focal features, or occurred more than once in 24 h. Routine haematological investigations after collection of blood samples were performed for all patients at time of admission or subsequent day of outpatient visit and of hospital admission. Total leukocyte count, Differential Leukocyte count, C-reactive protein, ESR, haemoglobin (Hb), Haematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), serum iron concentration, total iron binding capacity (TIBC), and plasma ferritin (PF) were collected for each patient and CSF examination was done to rule out CNS infections in indications such as age <12 month, complex febrile seizure or persistent lethargy.

All investigation done in central laboratory of SMS hospital Jaipur, CBC was done by automated differential cell counter, Ferritin estimation done by enzyme immunoassay procedure. Ferritin is acute phase reactant. We collected CRP, ESR for rule out effect of infection on ferritin, those cases and controls which had CRP positive and ESR >30 mm/hr were excluded.

Statistical analysis done by computer software SPSS, Discrete variables are expressed as counts (%) and compared using the Chi-square tests. Continuous variables are expressed as mean ± S.D. and compared by means of the unpaired, two-sided t test, Statistical significance was set at  $P < 0.05$ .

### III. Results

There were a total of 100 patients and 100 controls enrolled in both groups, out of them 16 cases from Study group and 15 from controls group, those who had either CRP Positive or ESR >30 mm in first hour or both were excluded. After Exclusion there were a total of 84 patients and 85 controls. Demographic data of cases and controls provided in Table 1; as shown in the cases and controls mean age were  $2.07 \pm 1.24$  and  $2.17 \pm 1.30$  ( $P > 0.05$ ) respectively. Both patients and the controls had a similar proportion of males (82.1% vs. 80%) and females (17.9% vs. 20%) ( $P > 0.05$ ). Seizure was most frequent on 12–24 months of age, and simple seizure was the most frequent type of seizures in all age groups. There was not statistically significant relationship between age groups and seizure types ( $P = 0.556$ ).

Data of the patient's hematologic status are provided in Table 2; as shown in the table, serum iron, and PF, Hb, MCV, MCH, and MCHC were significantly lower among the cases with FFC than in the controls, although TIBC was also lower among cases than controls, but differences were not statistically significant. The mean value in study group were significantly lower than Control group for Hb ( $9.39 \pm 1.75$  vs  $11.23 \pm 1.49$ ) ( $P < 0.0001$ ), MCV ( $70.47 \pm 7.91$  vs  $81.41 \pm 7.75$ ) ( $P < 0.0001$ ), MCH ( $22.26 \pm 3.70$  vs  $26.61 \pm 2.65$ ) ( $P < 0.0001$ ), MCHC ( $31.15 \pm 3.23$  vs  $32.92 \pm 2.0$ ) ( $P < 0.0001$ ), Ferritin <20ng/dl ( $11.77 \pm 2.91$  vs  $5.200 \pm 0$ ) ( $P < 0.01$ ), S. Iron ( $33.90 \pm 18.07$  vs  $43.36 \pm 12.94$ ) ( $P < 0.0001$ ) respectively.

Iron deficiency anaemia was more frequent among the cases with FFC, as compared to the controls, and its difference was statistically significant

**Table 1: Baseline characteristics of two groups**

Characteristic	Cases (n = 84)		Controls (n = 85)		Total	P value
	No.	%	No.	%		
Age						>0.05
6-12	25	29.76	23	27.1	48	
12-24	28	33.33	29	34.1	57	
24-36	15	17.85	14	16.4	29	
36-48	11	13.09	13	15.3	24	
48-60	5	5.9	6	7	11	
Sex						>0.05
Male	69	82.1	68	80	149	
Female	15	17.9	17	20	32	

**Table 2:**  
Comparison of cases and controls

	Cases (n = 84)	Control (n = 85)	P-value
Mean Hb (g%)	9.39 ± 1.75	11.23 ± 1.49	< 0.0001
Mean MCV (fl)	70.47 ± 7.91	81.41 ± 7.75	< 0.0001
Mean MCH (pg)	22.26 ± 3.70	26.61 ± 2.65	< 0.0001
Mean MCHC (g%)	31.15 ± 3.23	32.92 ± 2.0	< 0.0001
Mean serum iron (mg/dl)	33.90 ± 18.07	43.36 ± 12.94	< 0.0001
Mean TIBC (mcg/dl) >400	408.2 ± 4.60	412 ± 0.00	> 0.05
Mean PF (mg/l) <20ng/dl	11.77 ± 2.91	5.200 ± 0	< 0.01
Mean PF (mg/l) <30ng/dl	20.49 ± 6.73	22.22 ± 9.73	< 0.01

#### IV. Discussion

In our Study we examined the clinic-epidemiological profile of febrile seizure and association between iron deficiency anaemia and first febrile seizure. In this study we included 100 cases and 100 controls age groups of 6 month to 5 year old age. In both groups no significant difference in age and sex distribution. 16 children's from study and 14 childrens from control groups were either CRP positive or ESR > 30 or both excluded from study. The results of this study demonstrated the significantly lower level of haemoglobin, MCV, MCHC, MCH, serum iron, and PF, and significantly higher TIBC among the cases with FFC than in the controls

Piscaneet al<sup>2</sup>. Studied children's less than 2 years of age and reported that anaemia was significantly more common in cases than controls. Cut off value for MCV <70 fl in their study but did not analyse other blood indices; Hence our data represent close association between IDA and febrile seizure

Naveed-ur-Rehman and A.G. Billoo<sup>5</sup> in 2001 studied in 6 month to 5 year age on 60 patients (30 cases and 30 controls). And reported that Iron deficiency anemia was significantly more frequent among the case as compared to the controls as evident from parameters studied i.e. hemoglobin <10gm/dl (p<0.000), hematocrit <30% (P<0.01), MCV <70fl (P<0.002), MCH <24pg (P<0.001), and serum ferritin <110ng/dl (P <0.000). In their study they did not rule out effect of febrile illness on ferritin<sup>6</sup>.

Reverse observation had reported by Korbrinsky ET al<sup>16</sup> did a study to determine the effect of iron status on seizure threshold and documented that Iron deficiency may protect against the development of febrile seizures<sup>60</sup>

In present study is similar to study done by Naveed-ur-Rehman and A.G. Billoo<sup>5</sup> et al. Our observation Support the hypothesis provided by previous worker about role of iron deficiency that iron is involved in synthesis of Dopamine, Serotonin and probably GABA (gamma amino butyric acid)<sup>11</sup>, and myelin formation as well as in the metabolism of several other neurotransmitters<sup>12</sup>. Aldehyde and monoamine oxidases are reduced in iron deficiency anemia<sup>13</sup> which is (Iron deficiency anemia) common during the second and third years of life and has been associated with behavioral and developmental disturbances<sup>14</sup>.

#### V. Conclusion

Plasma ferritin level was significantly lower in cases as compared to controls suggesting that children who had febrile seizure are more iron deficient than the controls.

#### References

- [1]. Michael V. Johnston, Seizure in Childhood. Nelson: febrile seizure Text Book of Pediatrics. 17th edi. 2004: page 1994
- [2]. Pisacane A, Sansor R, Impagilazzo N, et al. Iron deficiency anaemia and febrile convulsion : Case control study in children under 2 years. BMJ 1996; 313: 343.
- [3]. Paradee Auvichayapat, Narong Auvichayapat et al. Incidence of Febrile Seizures in Thalassemic Patients. J. Med. Assoc. Thai 2004; 87(8): 970-3
- [4]. Daoud AS, Batieha A, Abu-Ekteish F, Gharaibeh N, Ajilouni S., Hijazi S. Iron status : a possible risk factor for the first febrile seizure. Epilepsia 2002; 43: 740-3.
- [5]. Naveed-ur-Rehman, A.G. Billoo. Association between iron deficiency anemia and febrile seizures. J. Coll. Phy. Surg. Pak. 2005, Vo. 15(5): 338-340.
- [6]. Berg AT, Febrile seizures and epilepsy, the contribution of epidemiology. Paediatr Perinatal Epidemiol 1992; 6: 145-52. Cross ref Michael V. Johnston, Seizure in Childhood. Nelson. Text Book of Pediatrics. 17th edi. 2004: page 1994

- [7]. Berg AT, Shinnar S, Shapiro ED, Salomon ME, Crain EF, and Hauser WA: Risk factors for a first febrile seizure: a matched case-control study. *Epilepsia* 1995; 36: 334-41.
- [8]. Habib Z, Akram S, Ibrahim S, and Hasan B, Febrile seizures: factors affecting risk of recurrence in Pakistani children presenting at the Aga Khan University Hospital. *J Pak. Med. Assoc.* 2003; 53: 11-7.
- [9]. Nelson KB, Ellenberg JH, Prenatal and perinatal antecedents of febrile seizures. *AnnNeurol* 1990; 27: 127-31.
- [10]. O.P.Ghai, Piyushgupta, V.K.Paul; Iron deficiency anaemia. *GHAJ ESSENTIAL PEDIATRICS*, Textbook of Paediatrics, 6th edition, page 122.
- [11]. Tany V, Mislus KP, Agarwal KN. Effect of early iron deficiency in rat brain on gamma-amino-butyric acid shunt in brain. *J. Neurochem* 1996; 46: 1670-4.
- [12]. Loscher W, Rating D, Siemes H, GABA in cerebrospinal fluid of children with febrile convulsion. *Epilepsia*, 1981; 22: 697-702.
- [13]. Parks YA, Wharton BA, Iron deficiency and the brain. *ActaPediatrScand* 1989; 55 (suppl 361): 71-7.
- [14]. Walter T, De Andraca I, Chadud P, Perales CG. Iron deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics* 1989; 84: 7-17.
- [15]. Parks YA Wharton BA. Iron deficiency anemia and brain. *ActaPediatrScandSuppl* 1989; 361: 71-7.
- [16]. Kobrinsky NL, YagerJy, Cheang MS, Does the iron deficiency raiser the seizure threshold. *J. Child neurol* 1995; 10:109.
- [17]. Commission on Epidemiology and Prognosis. International League against Epilepsy. Guideline for epidemiological studies on epilepsy. *Epilepsia*1993; 34: 592-595.