

ASSOCIATION BETWEEN IRON DEFICIENCY AND FEBRILE CONVULSIONS

Dr. Shaswat Dash

Assistant Professor, Dept of Paediatrics, 5 Air Force Hospital, Jorhat, Assam, India- 785005

Dr Premila Paul*

Professor & Consultant, Department of Paediatrics, VMMC and Safdarjang Hospital, New Delhi *Corresponding Author

ABSTRACT

Febrile convulsion is a convulsive episode usually occurring in age group 6 months to 36 months in association with febrile illness in absence of CNS infections or electrolyte imbalance^[1]. The incidence is 3 to 4% in young children^[2] and the recurrence rate is 30-40%^[3]. Iron deficiency is the most prevalent nutritional problem in developing countries^[4]. There is considerable evidence that iron is important for neurological functioning including neurotransmitter metabolism, myelin formation and brain energy metabolism^[5-8].

METHODS: A prospective case control study with 200 patients conducted in a tertiary care hospital showed an association between iron deficiency and febrile convulsion.

RESULTS: Mean serum iron levels in cases ($62.3 \pm 42.1 \mu\text{g/dL}$) was significantly less as compared in Controls ($71.5 \pm 25.6 \mu\text{g/dL}$) with P value of 0.04. Cut off for Iron Deficiency taken as $<50 \mu\text{g/dL}$ and the higher number of cases had levels below $50 \mu\text{g/dL}$ as compared to controls

CONCLUSION: 76% of children had lab evidence of Iron Deficiency and therefore it is suggested that Iron Deficiency should be taken care of timely to prevent Febrile Convulsions.

KEYWORDS : Febrile convulsions, Iron deficiency, anemia

INTRODUCTION

Febrile convulsion is the most common type of seizures with prevalence of 2-4% of all children in age group 6 months to 5 years. Iron is involved in the metabolism of several neurotransmitters, and monoamine and aldehyde oxidase were reduced in Iron Deficiency anaemia which is common during the second and the third year of life and has been associated with behavioural and development disturbances and there is altered regulation of oligodendrocyte iron uptake via transferrin and transferrin receptors. The restoration of brain iron with later aggressive dietary iron repletion also resulted in incomplete restoration of abnormalities in dopamine (DA) metabolism and in behaviours related to DA^[9] i.e., the sensitivity of a brain region to loss of iron during development is likely to be related to the regional development requirements for iron during that period. Alfredo Pisacane et al^[10] was first to show in 1997 that anemia was significantly more common in children 6- 24 months of age while Kobrinisky et al^[11] reported that iron deficiency raises the threshold for convulsions.

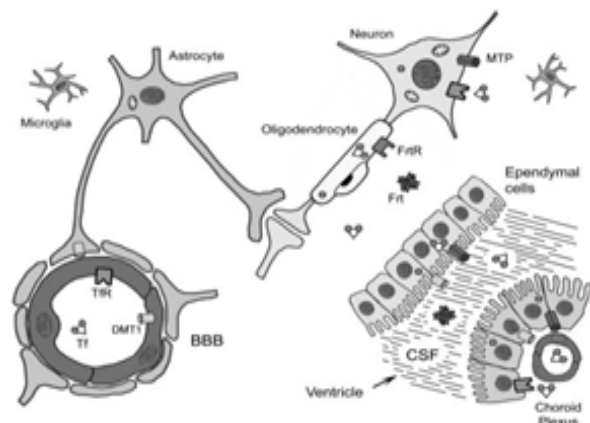


Figure 1: Cellular structure depicting neuroreceptors with iron transporter (DMT1: Divalent metal transporter)

Source: Domingo J Piñero and James R. Connor Iron in the Brain. An Important Contributor in Normal and Diseased States, *The Neuroscientist* 6(6): 435-453 · December 2000

METHODOLOGY

A prospective case control study was conducted in patients of Febrile Convulsions in age group between 6 months to 5 years who were admitted in Paediatrics Department

CASES: 100 patients of Febrile Convulsions of both the sexes in age group 6 months to 5 years

CONTROLS: 100 age and sex matched patients with fever and no convulsions. Confounding factors like nutrition, socioeconomic status, worm infestation, recurrent infections were taken care off in both the groups. Patients with CNS infection, history of non-Febrile Convulsions, underlying blood disorder, known case of epilepsy and developmental delay were excluded.

EXCLUSION CRITERIA: Children presenting with CNS infection, history of non-Febrile Convulsions, chronic multi-system disease, underlying blood disorder, children who received blood transfusion for anemia, hematologic malignancy, on iron supplementation, known case of epilepsy, had developmental delay were excluded from study.

All cases subjected to Haematological investigation and Iron profile: Serum Iron, TIBC (Total Iron Binding Capacity) and Serum ferritin. In presence of fever, a higher cut-off value of serum ferritin and iron is used which is $<30 \mu\text{g/dL}$ and $<50 \mu\text{g/dL}$ respectively were considered. Cases and Controls were compared with respect to blood indices and serum ferritin.^[4]

Iron deficiency anemia was defined as^[2]

- Haemoglobin $<11 \text{g/dl}$
- MCV $<70 \text{fl}$ (70-86)
- Serum Iron $<50 \mu\text{g/dL}$
- TIBC $>250 \mu\text{g/dL}$ (250-400)
- Serum ferritin $<30 \mu\text{g/dL}$ (7-140)

Sample size was calculated using Epi Info program based on the assumptions that alpha error 8%, and prevalence of exposure (Iron Deficiency) in the non-ill group (controls) 30% 13 Data were entered in MS Excel and analysis was done using SPSS Version 20. Analysis includes Chi square analysis for continuous variable and non-parametric tests for discrete variables and p value was taken as <0.05 to be statistically significant.

RESULTS

Table 1 Comparison of means of Hb, RBC indices and iron studies in cases and controls

PARAMETER	CASES	CONTROLS	P VALUE
AGE (years) median [IQR]	2.7	2.69	0.16
Mean Hemoglobin (g/dl)	9.5±1.8	11.94±1.9	0.001
Red Cell Distribution Width (%)	18.1±6.3	13.1±5.6	0.001
Mean Corpuscular Volume (fml)	71.1±8.3	75.1±9.4	0.001
Mean Corpuscular Hemoglobin(pg/cell)	25.08±5.4	27.05±4.1	0.032
Mean Corpuscular Hemoglobin Concentration (% Hb/cell)	30.5±4.4	30.4±3.9	0.64
Serum IRON (µ g/dL)	62.3±42.1	71.5±25.6	0.04
TIBC (µ g/dL)	265.87±59.3	214.7±40.9	0.003
Serum FERRETIN (µ g/L)	42.83±38.1	60.06±49.8	0.004

FIGURE – 2 GRAPHICAL REPRESENTATION

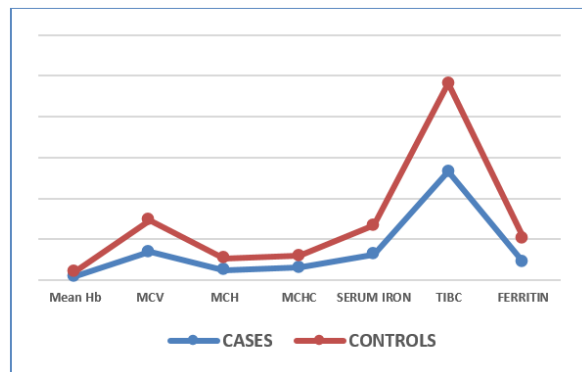


Table 2 : Association of degree of fever with type of convulsions

There was no correlation between degree of fever and occurrence of simple or complex Febrile Seizures (P VALUE 0.21)

DEGREE OF FEVER	SIMPLE N=74	PERCENT	COMPLEX N=26	PERCENT	TOTAL
<390c	14	13.7	8	30.7	28
>390c	60	81	18	69.2	13
TOTAL	74	100	26	100	100

DISCUSSION

Despite the coincidence of Iron Deficiency anemia with Febrile Convulsions little work has been done to find out any association between the Iron deficiency and Febrile Convulsions. Results of most available studies are conflicting however major trend is towards Iron Deficiency as a predisposing factor for Febrile Convulsions.^[11-13] Some studies have described Iron Deficiency is less common in patients with Febrile Convulsions.^[14-15]

The occurrence of seizures was correlated with the degree of fever 78% occurred when the temperature was more than 39^oc. Bidabadi^[16] quoted that the mean of temperature peak on admission was significantly higher in the FFC group (38.74 ±0.76 8C) compared with the controls (38.2±0.67 8C)(P < 0.0001).However other studies by Modaresi et al, Bidabadi et al, Vaswani et al and Daud et al^[12,16] did not show any statistical significance.

In our study the family history of seizures was compared with type of seizures and it was not significant All the cases and controls were subjected to Mean Corpuscular Volume (MCV),

Mean Corpuscular Haemoglobin(MCH).the cut off value for MCV was taken as 70fml. In our study the mean of MCV in cases was 71.1±8.3 fml while of the controls was 77.2±8.8 fml and the difference was significant with the p value of 0.001. The studies by Bidabadi et al, Vaswani et al, Modaresi et al and Daud et al comparing MCV and MCH did not show any statistical significance^[12,16]

The mean MCH in cases was 71.1±8.3 pg while in controls was 27.05±4.1pg with p value 0.032.Difference in cases and controls were statistically significant. Similar findings were seen in study by Modaresi et al while the other studies did not show any significant difference.^[12]

The studies by Bidabadi et al, Vaswani et al, Modaresi et al and Daud et al^[11-13] comparing mean serum ferritin in cases and controls also showed statistically significant difference.

Table no. 18 Comparison of the different studies on the basis of Mean serum ferritin levels amongst the cases and controls

Mean serum ferritin	CASES (µg/dL)	CONTROLS (µg/dL)	P VALUE
Present	42.8±38.17	60.06±49.8	0.004
Bidabadi	100.23 ±114.23	75.27 ± 50.80	0.005
Vaswani	31.9 ± 31.0	53.9 ± 50.5	0.003
Daud	29.5 ± 21.3	53.3± 37.6	0.0001
Modaresi	51.87 ± 41.03	81.25 ± 85.96	0.00

Studies by Modaresi et al, Bidabadi et al, Vaswani et al and Daud et al^[11-13] showed significant Iron Deficiency in the form of low serum iron levels, high TIBC and low serum ferritin levels signifying Iron Deficiency as a risk factor for Febrile Convulsions.

DEGREE OF FEVER	SIMPLE N=74	PERCENT	COMPLEX N=26	PERCENT	TOTAL
<390c	14	13.7	8	30.7	28
>390c	60	81	18	69.2	13
TOTAL	74	100	26	100	100

CONCLUSION

In our study we tried to find the association of iron levels in children with febrile seizures. Mean serum iron levels in cases(62.3±42.1µg/dL) was significantly less as compared in controls(71.5±25.6µ g/dL) with P value of 0.04. Similar findings also seen in mean TIBC and serum ferritin which was higher in controls than cases.

Mean haemoglobin was lower in cases(9.94±1.80 gm/dl) as compared to controls (11.44±1.9 gm/dl) and the difference was statistically significant (0.001).Mean MCV compared among cases(71.1±8.3 fml) and controls(77.2±8.8 fml) p value (0.001) was significant in age group 1year to 5 year. All parameters when compared show cases had significant Iron Deficiency as compared to controls.

RECOMMENDATION

In a child who has features suggestive of Iron deficiency and fever more than 39^oc with a family history of febrile convulsion is likely to have Febrile Convulsions.

Iron deficiency is a possible risk factor for the occurrence of first Febrile Convulsions however the type of convulsion cannot be predicted.

76% of children had lab evidence of Iron Deficiency and therefore it is suggested that Iron Deficiency should be taken care of timely to prevent Febrile Convulsions.

REFERENCES:

1. Robert S. Fisher, Walter van Emde Boas, Warren Blume, Christian Elger, Pierre Genton, Phillip Lee, and Jerome Engel, Jr.Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE)

- and the International Bureau for Epilepsy (IBE) *Epilepsia*, 2005 46(4):470–472
2. Johnston MV. Seizures in childhood. In: Kleigman RM, Behrman RE, Jenson B, Stanton BP Nelson. *Text Book of Pediatrics* 19th Edition Philadelphia: Saunders Elsevier; 2007. p.2457-8.
 3. Habib Z, Akram S, Ibrahim S, Hasan B. Febrile Convulsions: Factors affecting risk of recurrence in Pakistani children presenting at The Agha Khan University Hospital. *J Pak Med Assoc* 2003;53:11–7.
 4. World Health Organization. *Iron Deficiency Anemia. Assessment, Prevention and Control. A Guide for Program Managers.* WHO/NHD/013; Geneva: 2001
 5. Rao, R. & Georgieff, M. K. (2001) Neonatal iron nutrition. *Semin. Neonatol.* 6: 425–435.
 6. Roncagliolo, M., Garrido, M., Walter, T., Peirano, P & Lozoff, B. (1998) Evidence of altered central nervous system development in infants with Iron Deficiency anemia at 6 mo: delayed maturation of auditory brainstem responses. *Am. J. Clin. Nutr.* 68: 683–690.
 7. Shankar, N., Tandon, O. P, Bandhu, R., Madan, N. & Gomber, S. (2000) Brainstem auditory evoked potential responses in iron deficient anemic children. *Indian J. Physiol. Pharmacol.* 44: 297–303.
 8. Lozoff, B., Brittenham, G. M., Wolf, A. W., McClish, D. K., Kuhnert, P. M. & Jimenez, E. (1987) Iron deficiency anemia and iron therapy: effects on infant developmental test performance. *Pediatrics* 79: 981–995.
 9. Pinero, D. J., Jones, B. & Beard, J. L. (2000) Alterations in brain iron metabolism in response to dietary iron changes. *J. Nutr.* 130: 254–263.
 10. Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A, et al. Iron deficiency anaemia and Febrile Convulsions: case-control study in children under 2 years. *BMJ* 1996;313(August (7053)):343.
 11. Kobrinsky NL, Yager JY, Cheang MS, Yatscoff RW, Tenenbein M. Does Iron Deficiency raise the seizure threshold? *J Child Neurol.* 1995;10(2):105
 12. Mohamadreza Modaresi Touran Mahmoudian, Omid Yaghini, Roya Kelishadi Homayoun Is Iron Insufficiency Associated With Febrile Seizure? *J Comp Ped.* 2012;3(1):21-24. DOI: 10.5812/jcp.6946
 13. Rajwanti K Vaswani, Praveen G Dharaskar, Swati Kulkarni And K Ghosh. Iron Deficiency as a Risk Factor for First Febrile Seizure, *Indian Pediatrics*, 2010, Volume 47_May 17: 438
 14. Salehi omran, Tamaddoni A, Nasehi MM, Babazadeh H, Alizadeh navaei R. Iron Status In Febrile Seizure: A Case-Control Study *Iran J Child Neurology* Dec 2009
 15. Hojjat Derakhshantafar, Ali Abaskhanian, Hosein Alimohammadi, Mona ModanlooKordi Association between Iron Deficiency anemia and febrile seizure in children *Medicinski Glasnik*, August 2012 Volume 9, Number 2
 16. Elham Bidabadi, Mehryar Mashouf Association between Iron Deficiency anemia and first febrile convulsion: A case-control study *Seizure* 18 (2009) 347–351