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ASSOCIATION BETWEEN IRON DEFICIENCY ANEMIA AND FEBRILE SEIZURES IN CHILDHOOD

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ABSTRACT

INTRODUCTION: Febrile seizures are the most common form of childhood seizures, occurring in 2 to 5% of children. The peak incidence is at the age of approximately 18 months, with recurrent episodes occurring in one third of patients. Iron deficiency is the most common nutritional disorder affecting at least one third of world's especially between 6 and 24 months, this study was taken up to determine the association between febrile seizures and Iron deficiency as defined by the hematological parameters, which is a very important investigation in a resource limited country like India.

AIMS: Prospective study to determine the association between iron deficiency anemia and febrile seizures in the age group 6 to 60 months.

METHODS AND MATERIALS: study design Case control study. Study period : 7 months period from March 2014 to September 2014 Children of age group 6 months to 60 months presenting with febrile seizures to the pediatric emergency department and wards of the hospital were included

RESULTS: 80% of the study population within seizure group was between 6 months and 36 months. There was no significant gender predisposition for febrile seizures, and both genders were affected more or less in equal proportion. Family history of febrile seizures was a significant non modifiable risk factor in the seizure group. 21.4% of seizure group had a family history of febrile seizures in first degree relatives. There was a significant difference in the value of Hb , MCH, serum iron, TIBC and RDW among the seizure group as compared to control group. There was a mean difference of 5% of MCV between the seizure group and controls, which was not statistically significant in the study.

CONCLUSION: Hematological parameters have been demonstrated to be sensitive and specific in children, and stable in the presence of febrile illness. Complete Blood count, being a simple and feasible investigation, can be used to screen individuals with iron deficiency in simple febrile seizures, for making a decision to start iron supplementation.

KEYWORDS : Febrile seizures, Iron deficiency anemia, Fever, Hemoglobin, Hematological parameters

1. INTRODUCTION

Febrile seizures are the most common form of childhood seizures. [1] These episodes are agonizing to the parents and child and therefore can cause psychological trauma to both. Although frightening to the caregivers, they are benign, and the risk of subsequent epilepsy population. Febrile convulsions have been studied extensively over the past two decades, and a large body of literature now exists to help practitioners assess the risks associated with such presentations. Currently identified risk factors for febrile seizures include having a first or second degree relative with a history of febrile seizure, maternal smoking in pregnancy, low birth weight, neonatal stay of > 30 days, attendance at day care, increased number of febrile illnesses per year,Fever > 39.4, and particular infectious illnesses. [2] Genetic factors contribute significantly to the etiology. Most studies have supported a polygenic or multi factorial model; with an estimated heritability of 75% [3-5] despite these studies the risk factors remain largely unknown.Iron deficiency is the most common nutritional disorder affecting at least one third of world's especially between 6 and 24 months. [6-9] Iron deficiency is defined as a condition in which there are no mobilizable iron stores and in which signs of a compromised supply of iron to tissues, including the erythron, are noted. [10] The more severe stages of iron deficiency are associated with anemia and though anemia is the most common manifestation of Iron deficiency, other effects of Iron deficiency of various tissues and organs are still under recognized and needs more researches in the field. Impaired brain developments along with cognitive, behavioral and psychomotor manifestations are still under recognized to a larger extent. It has been shown by various studies that some of these impairments on the brain during the first two years, i.e. the growth spurt period of brain may be irreversible. Among numerous biological effects of iron, there is considerable evidence that iron is also important for the neurological functioning, which include neurotransmitter metabolism, myelin formation, and brain energy metabolism. Iron-deficient animals show alterations both in neurotransmitters and behavior that do not usually respond to iron replenishment .As iron is important for the growth of neurotransmitters and various enzymes, iron deficiency may lower the seizure threshold.In a resource country like India, it is not always feasible to get the biochemical parameters of Iron stores in the body, and hematological parameters available in a complete blood count is not interpreted in a systematic way to screen Iron deficiency anemia. There is no single standard test to assess iron deficiency without anemia.[10] so as a result of this many Microcytic hypochromic anemia's of which Iron deficiency anemia being the most common cause, go unnoticed and untreated. So this study was taken up to determine the association between febrile seizures and Iron deficiency as defined by the hematological parameters, which is a very important investigation in a resource limited country like India. And if such an association exists, iron deficiency can be addressed at an earlier stage which may be helpful for prevention of simple febrile seizures.

2. AIM

Prospective study to determine the association between iron deficiency anemia and febrile seizures in the age group 6 to 60 months.

3. METHODS AND MATERIALS

Study desing: Case control study study period: 7 months period from March 2014 to September 2014 subjects: This was a prospective case control study done in a tertiary care hospital (chengalpattu Medical Hospital) between the periods March 2014 to September 2014. Ethical clearance was obtained for the study from the Ethical Committee of the Hospital. Inclusion Criteria**:**Children of age group 6 months to 60 months presenting with febrile seizures to the pediatrics emergency department and wards of the hospital during the study period.Diagnostic criteria for simple febrile seizures (based on AAP Clinical Practice Guidelines: 2008) included seizures associated with fever and the seizures were generalized, short duration (less than 15 minutes), no recurrence of seizures within 24 hours, child is otherwise neurologically healthy and without any neurological abnormality before and after the episode of seizures, with age group between 6 months to 5 years. Exclusion Criteria: Children with age less than 6 months and more than 60months. children with Development delay**,** Central neurons system infections**,** Past history of non febrile seizure**,** Chronic multisystem diseases**,** Diagnosed cases of other hematological problems like hemolytic anemia's, bleeding (or) coagulation disorders, hematological malignancies (or) Children on Haematinics were excluded After informed consent, detailed history was elicited and physical examination was done Hospital records were also examined for relevant data. Blood Investigations done to diagnose Iron deficiency included hemoglobin (Hb) in gm/dl estimation and mean corpuscular volume (MCV) in Fl, Mean corpuscular Hemoglobin in (MCH) in Pg and red cell distribution width (RDW) in

percentage, Reticulocyte count in percentage, serum Iron in (Mg/dl) (Microgram/ deciliter, serum total iron binding capacity in Microgram/ deciliter and peripheral smear study. The investigations was carried out using an automated Hematology Analyser. Iron deficiency was diagnosed by hematologic investigations of hemoglobin value <11gm/ dl, MCV <70 Fl, MCH< 27 Pg and RDW > 15%, serum Iron < 60 Mg/dl, TIBC > 400 Mg/dl, Reticulocyte count Normal (2-2.5%). Peripheral smear-shows microcytic hypochromic. Other variables studied included age of the child, sex, family history of febrile seizure in first degree relatives, neonatal hospital admissions (NICU or special care nursery admissions), permaturity (<37 weeks gestational),nature of underlying illness and immunization status of child.The controls were selected from the same setting and included febrile children of age group 6 months to 60 months who presented with short duration fever (<3 days) but without seizures to the outpatient department or wards. Cases and controls were selected in 1:1 ratio. No matching was done.

SAMPLE SIZE: Based on the results form available publications in India, and with 90% power and 99% confidence minimum sample size in each group come to 70 each. Data were entered in MS Excel, cleaned and checked. The statistical analysis was carried out using statistical software SPSS19.

STATISTICS ANALYSIS: The categorical variables were expressed as Frequency and percentage. The quantity variables were expressed as mean ± standard deviation. Descriptive statistics were used to evaluate baseline characteristic

4. RESULTS

The mean age of seizure group and controls were 20.73 ± 12.43 and 23.10 ± 14.17 months respectively. Also both the groups had almost similar proportions of males (51.4% and 48.6%) and Females (61.4%) and (38.6%) Also the mean temperature in the seizure group was found to be 100.36 ± 0.55 . 80% of the Study populations in the seizure group were between 6 months and 36 months of age, with the mean of 20.73 ± 12.43 months and there was no significant difference in gender predilection. In this study 42.9% of seizure group had peripheral smear shows microcytic hypochromic, whereas only 10% of controls were peripheral smear shows microcytic hypochornic anemia. This was found to be statistically significant (P-0.000). respiratory tract infections, viral fever and acute diappoheal disease were the most frequent underlying illnesses for fever in cases, whereas Respiratory tract infections and viral fever were more among the control group.Other few cases have diagnosed urinary tract infection.Also acute respiratory tract infecctions were the most frequent

causes for fever in control In this study 21.4% of seizure group had a family history of febrile seizures in first degree relatives, whereas only 2.9% of controls were having a positive family history (P-0.000) Family history of febrile seizures, which most likely presents a genetic susceptibility to seizures with fever, may be a significant non modifiable risk factor. This study also demonstrates that Iron deficiency as defined by hematological parameters i.e., Hb, MCV, MCH, RDW, serum Iron, serum ITBC, Reticulocyte count and peripheral smear was significantly associated with seizure group (43%) when compared with controls (10%) (P value 0.0001) The results of this study demonstrated significantly lower levels of HB, MCH, Serum Iron, Serum TIBC and higher values of RDW among the cases with febrile seizures that in the controls (P<0.05). This was found to be statistically significant. MCV was low in cases as compared with controls, but a mean difference of 5% of MCV between the seizure group and controls, but differences failed to attain statistical significance

FIGURE 1: PERIPHERAL SMEADISTRIBUTION

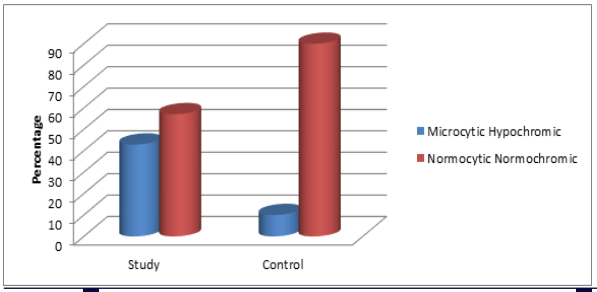

FIGURE 2: DISEASE DISTRIBUTION

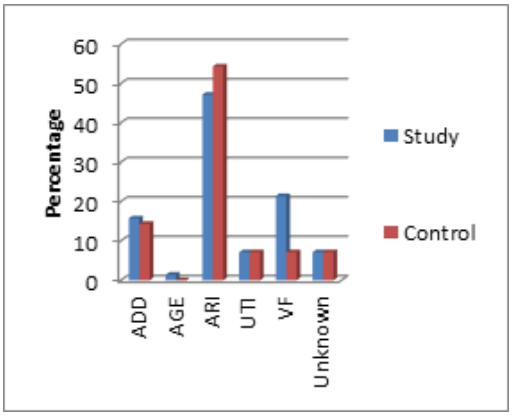

FIGURE 3: FAMILY HISTORY OF FEBRILE SEIZURE

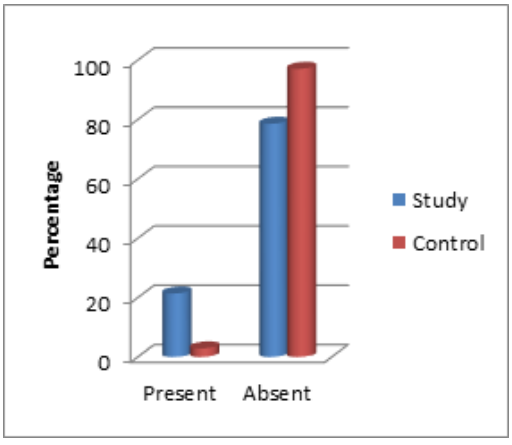

FIGURE 4 : IRON DEFECIENCY ANEMIA IN STUDY GROUP

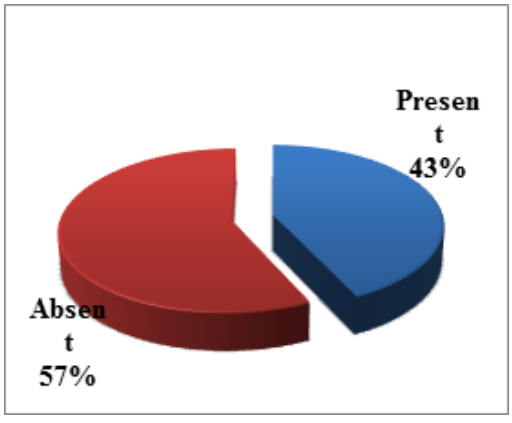

FIGURE 5: IRON DEFECIENCY ANEMIA IN CONTROL GROUP

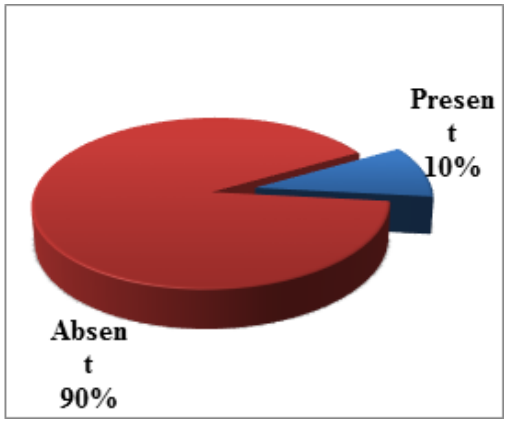

TABLE 1 COMPARISON OF CASES AND CONTROLS WITH RESPECT TO VARIABLES.

	Study	Control	P value
Age	20.73 12.43	23.10 14.17	0.294
HB	10.62 1.39	11.43 0.81	<0.05
MCV	76.06 5.42	78.63 3.24	0.001
MCH	25.01 3.13	26.56 1.23	<0.05
RDW	14.77 1.38	13.90 0.89	<0.05
Reticulocyte Count	2.16 0.24	2.19 0.12	0.504
Serum Iron	50.89 25.99	78.92 19.33	<0.05
TIBC	508.15 145.18	412.24 76.08	<0.05
Temperature (F)	100.36 0.55	99.91 0.29	0.000

5. DISCUSSION

In this study, 80% of the study population within seizure group was between 6 months and 36 months. There was no significant gender predisposition for febrile seizures, and both genders were affected more or less in equal proportion. Pisacane et al. [11] in a case-control study with 146 cases and 146 controls, with age of 6-24 months, reported a significantly higher rate of iron deficiency anemia among children with first episode of febrile convulsions than in controls. Iron status was measured by HB, MCV and serum Iron. Dawn et al. [12] in a retrospective case control study of 361 cases and 390 controls in the age group 6 to 36 months found that children with febrile seizure were almost twice as likely to be iron deficient as those with febrile illnesses alone. Iron status was measured by HB, MCV and RDW. Daoud et al. [13] in a case-control study with 75 cases and 75 controls in the age group of 3-72 months, demonstrated that only low PF level is associated with and may play a role in first episode of febrile convulsions, with lack of significant differences in HB, MCV and MCH. Iron status was measured by HB, MCV, MCH and serum Ferritin. At the same time Kobrinsky et al. [14] in a case-control study with 25 cases and 26 controls in the age group of 6-36 months concluded that children with febrile seizures were less likely to be iron deficient and iron deficiency may protect against the development of febrile convulsions. Similarly, Elham Bidabadi a, Mehryar Mashouf, [15] in a case-control study with 200 cases and controls suggested that iron deficiency anemia was less frequent among the cases with febrile convulsion, as compared to the controls, and there is not a protective effect of iron deficiency against febrile convulsions. Bidabadi et al,[15] in a case control study with 200 cases and 200 controls suggested that iron deficiency anemia was less frequent among the cases with febrile convulsions in age group of 6months to 5 years. In this study, the amount of RBC, serum iron and plasma ferritin were high and TIBC was low among the cases with first febrile convulsions than in the controls. The amount of Hb , HCT, MCV, MCH, and MCHC were high among the cases than controls, but differences were no statistically significant. Iron deficiency anemia was less frequent among the cases with febrile convulsions, as compared to the controls, and its difference was not statistically significant. Derakshanfar H et al[16] in this case control study done in 500 children with febrile seizure (cases) and 500 children without febrile seizures(controls) in the age group of 6-60 months, suggested that the risk of febrile seizures in anemic children is less common than non- anemic ones. The amount of hemoglobin, hematocrit, MCV, MCH, MCHC, Rbc count, serum iron and plasma ferritin were significantly higher and TIBC was significantly lower among the cases with febrile convulsions than the controls. The incidence of iron deficiency anemia was significantly higher in controls compared with the cases (p less than 0.016). The mean of temperature peak on admission was significantly higher in the febrile convulsions cases than in controls. Hartfield DS et al [17] conducted a retrospective case control study with 361 cases with febrile seizures and 390 controls presented with febrile illness without seizures in the age group of 6 to 36 months. This study used MCV, RDW and hemoglobin to determine the iron status. The results demonstrated that 9 % of cases had iron deficiency anemia compared to 5 % of controls and 6% had iron deficiency compared to 4% of controls. The conditional logistic regression odds ratio for iron deficiency in patients with febrile seizures was 1.84. The study conclusion is that febrile seizures were almost as twice common in iron deficiency anemia . The results also suggested that screening for iron deficiency anemia should be considered in children presenting with febrile seizures. In this study the majority of febrile convulsions occur between 6 months and 36 months of age, with the mean of 20.73 ± 12.43 months and there was no significant difference in sex predilection. Also, family history of febrile seizure, which most likely represents a genetic susceptibility to seizures with fever, were higher among seizure group ($P < 0.000$).The results of our study demonstrated significantly lower levels of Hb, MCH, serum Iron, TIBC and higher values of RDW among the seizure group when compared with controls ($P < 0.05$). The amount of MCV, Hct, MCHC and RBC count were also lower in the seizure group as compared with controls, but differences failed to attain statistical significance. There was a mean difference of 5% of MCV between the seizure group and controls, which was not statistically significant in the study. In our study 42.9% of seizure group had peripheral smear shows microcytic hypochromic, whereas only 10% of controls were peripheral smear shows microcytic hypochromic anemia. This was found to be statistically significant (P – 0.000)The study also demonstrates that Iron deficiency as defined by hematological parameters i.e., Hb, MCV, MCH, Serum Iron, TIBC, RDW and peripheral smear was significantly associated with cases (43%) when compared with controls (10%) (P value 0.0001).Respiratory tract infections were the most common underlying illness among the seizure group, followed by viral fevers, acute diarroheal diseases and urinary tract infections, in the study. Family history of febrile seizures was a significant non modifiable risk factor in the seizure group. 21.4% of seizure group had a family history of febrile seizures in first degree relatives.There was a significant difference in the value of Hb, MCH, serum iron, TIBC and RDW among the seizure group as compared to control group. There was a mean difference of 5% of MCV between the seizure group and controls, which was not statistically significant in the study. Iron deficiency anemia as defined by hematological parameters i.e., Hb, MCV, MCH, serum iron, TIBC, Retiulocyte count, RDW and peripheral smear with simple febrile seizures in the age group 6-60 months. Complete Blood count, being a simple and feasible investigation, can be used to screen individuals with iron deficiency in simple febrile seizures, for making a decision to start iron supplementation. Our study concludes that 80% of the study population within seizure group was between 6 months and 36 months. There was no significant gender predisposition for febrile seizures, and both genders were affected more or less in equal proportion. Respiratory tract infections were the most common underlying illness among the seizure group, followed by viral fevers, acute diarroheal diseases and urinary tract infections, in the study. Family history of febrile seizures was a significant non modifiable risk factor in the seizure group. 21.4% of seizure group had a family history of febrile seizures in first degree relatives. There was a significant difference in the value of Hb, MCH, serum iron, TIBC and RDW among the seizure group as compared to control group. There was a mean difference of 5% of MCV between the seizure group and controls, which was not statistically significant in the study. Iron deficiency anemia as defined by hematological parameters i.e., Hb, MCV, MCH, serum iron, TIBC, Retiulocyte count, RDW and peripheral smear with simple febrile seizures in the age group 6-60 months.Complete Blood count, being a simple and feasible investigation, can be used to screen individuals with iron deficiency in simple febrile seizures, for making a decision to start iron supplementation.Role of correction of Iron deficiency in preventing simple febrile seizures in children needs to be studied.

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This study has some limitations. A case-control study of this nature can introduce selection bias because all cases of febrile seizures may not be coming to the hospital. So study be misleading if cases were identified from hospital admission to hospital was influenced not only

by the presence and severity of disease but also by other variables, such as social class. Iron status of the body was not determined, as the study was planned to identify iron deficiency, as defined by the hematological parameters. So the specificity of diagnosing iron deficiency was less because other cases of microcytic hypochromic anaemic like Beta thalassemia and lead poisoning could not be ruled out in these cases. Accordingly, there is a need for further large cohort study for this problem.

The strength of this study included standardized criteria for diagnosing febrile seizures, and iron deficiency anemia defined by hematological parameters, concurrent enrollment of cases and controls, and no recall bias regarding exposure. Parameters such as ferritin, transferring saturation and free erythrocyte protoporphyrin were not taken into consideration. These measurements of iron status are influenced by infections and therefore are not reliable indicators of iron status in the settings in the settings of acute infections. [18] Hematological parameters have been demonstrated to be sensitive and specific in children, and stable in the presence of febrile illness, [19] and are therefore strength of the study design.

Furthermore, whether correction of iron deficiency reduces the incidence of febrile seizures is an attractive hypothesis that needs to be tested.

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