Original Research Article

A Hospital Based Case Control Study on Correlation Between Simple Febrile Seizure and Iron Deficiency Anaemia

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Abstract

Febrile seizure (FS) is the most common convulsive disorder in children, which affects 2-5% of children aged between 3 to 60 months. Among the numerous biological effects of iron, there is considerable evidence that iron is also important for neurological functioning. **Aims and Objectives:** To assess and evaluate any possible association between febrile convulsion and iron deficiency anaemia. **Materials and Methods:** This case-control study involved 300 children aged from six months to 5 years, hospitalized in the pediatrics ward of NMCH, Patna from May 2019 to November 2020. They were divided into two groups of 150 children each. In the case group children having simple febrile convulsion were kept and the control group had children with fever of less than 3 days duration but without febrile convulsion. **Result:** The risk of simple febrile seizure was 1.86 times more among the patients with level of hemoglobin < 11 gm/dl as compared with the patients with level of hemoglobin≥11 gm/dl [OR-1.76(1.01, 3.08); p= 0.04] and the risk was significant. **Conclusion:** we concluded that iron deficiency anemia (IDA) was more frequently seen among children with FS than those with febrile illness alone. .All the investigations done also suggested that iron deficient children are more prone for febrile seizures and hence prophylactic iron supplementation in iron deficient anaemic children can probably avert first febrile convulsions.

Keywords: Iron deficiency, anemia, Febrile seizures.

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Introduction

Febrile seizure (FS) is the most common convulsive disorder in children, which affects 2-5% of children aged 3 to 60 months [1]. Although FS is benign and rarely leads to brain damage, it causes emotional, physical, and mental damages, which are stressful for parents, and affects quality of life of entire family [1]. Many studies have tried to find its risk factors, because of its relation to epilepsy (2-4%) , it can lead to frequent hospitalization, financial burden to families and the society, and likelihood of its recurrence (30% and 50% after the first and the second occurrences, respectively)[1]. Among the numerous biological effects of iron, there is considerable evidence that iron is also important for neurological functioning [2,3]. Such functions include neurotransmitter metabolism [4,5,6], myelin formation[7] and brain energy metabolism[8,9]. In rodent model, iron deficiency affects regional monoamine metabolism, in part through iron-dependent enzymes such as tryptophan hydroyxlase (for serotonin) and tyrosine hydroxylase (for dopamine and norepinephrine) [10]. Recent research shows that iron deficiency also results in elevations in extracellular dopamine and norepinephrine and reductions in D1 and D2 receptors and all monoamine transporters [3,4,5]. Iron deficiency decreased the expression of cytochrome c oxidase, a marker of neuronal metabolic activity [6].

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Serial neurometabolic assessment of the hippocampus in the iron deficient rat pup showed elevations in intracellular glutamate, phosphocreatine, and phosphoryl-ethanolamine concentration [7]. Gestational iron deficiency induces changes in the dendritic structure, as assessed by microtubule associated protein 2 expressions. The role of iron in myelination of the rodent brain has been known for several decades. Potential explanations include fundamental changes to early preoligodendrocyte and oligodendrocyte populations and altered regulation of oligodendrocyte iron uptake via transferrin and transferrin receptors [8,9]. Most human studies on developmental and behavioral effects of iron deficiency focus on the infancy period of peak prevalence, which is 6–24 months. Iron deficiency anemia patients have shown an altered rapid eye movement density in active sleep [3], poorer recognition memory with event-related potentials [3], and altered electroencephalographic frontal asymmetry [3]. Affective changes in iron deficiency anemia infants, such as wariness, hesitance, decreased positive effect, and social interaction, are seen. Recent studies of auditory evoked potential changes in iron deficient infants point to possible irreversibly slowed central processing [3,4]. A basic principle of fetal/neonatal iron biology is that iron is prioritized to red cells at the expense of other tissues, including brain. When iron supply does not meet iron demand, the fetal brain may be at risk even if the infant is not anemic [5]. The purpose of the present study was to assess the relation, if any, of iron status with first febrile convulsion.

Aims And Objectives

To assess and evaluate any possible association between febrile convulsion and iron deficiency anaemia.

Materials And Methods

This case-control study involved 300 children aged from six months to 5 years, hospitalized in the pediatric ward of NMCH, Patna from May 2019 to November 2020. They were divided into two groups of 150 children each. In the case group children suffering from simple febrile convulsion and the control group having children with fever caused by any factor and without febrile convulsion and less than 3 days duration were taken. Children who had previous episodes of febrile convulsion, those with a diagnosed organic cause of convulsion, when the convulsion was a combined form, or there were delayed development, neurologic defects, central nervous system infection, and when the parents did not co-operate well, were excluded from the study. At hospitalization, the children underwent careful physical and nervous system examinations by the assistants and emergency personnel of the pediatric ward, especially with respect to symptoms of meningeal irritation. Axillary temperatures of these children were measured at hospitalization and if these temperatures (when 0.5 degree was added to them) exceeded 38°C, they were included in the study. As an antipyretic, 10-15 mg/kg acetaminophen was administered every 4-6 hours for children whose body temperature exceeded 38°C. The case and control groups were matched with respect to age, sex, body temperature, development curve, and history of treatment with iron supplements. The family histories of children with respect to febrile convulsion and anemia were also checked and the related information was recorded. A convulsion accompanied by fever that lasted less than 15 minutes without local and focal symptoms was considered as a simple febrile convulsion. In cases where the presence of meningitis was suspected, a sample of the cerebrospinal fluid would be taken and, if meningitis was diagnosed, the child would be excluded from the study. After normalization of body temperature of all the affected children, in order to find cases of iron deficiency anemia, 5 ml blood sample was taken from each child for a complete blood count (CBC) and to measure the levels of serum iron, plasma ferritin, and TIBC (total iron binding capacity). All the parents or guardians of the sick children gave their written consent to their children taking part in the study; they could withdraw from the study anytime they desired. The researchers in this study were committed to the Helsinki Declaration at all stages of the study. Descriptive, distribution, and Chi-square tests were performed for the qualitative variables, and the independent **t**-student test was carried out (given that normal distribution was used in the K-S test) and **P** values less than 0.05 were considered significant.

Inclusion criteria : -

1. In case group children of age group of 6 months to 5years presenting with simple febrile seizures were kept.
2. Concurrent Control groups included febrile children of age groups between 6 months to 5 years who presented with short duration fever (<3 days) but without seizures.

Exclusion criteria : -

1. Atypical febrile seizures.
2. Afebrile seizures.
3. Central nervous system infection.
4. Chronic Neurodevelopment problems.
5. Other hematologic problems like chronic hemolytic anemias, bleeding or coagulation disorders, haematologic malignancy.
6. Those who were on iron supplementation.
7. Very sick children

Statistical Analysis

Statistical Analysis was performed with help of Epi Info (TM) 3.5.3 of the Centers for Disease Control and Prevention (CDC).

Using this software, basic cross-tabulation and frequency distributions were prepared. χ^2 test was used to test the association between different study variables under study.

Test of proportion (Z-test) was used to test the significant difference between two proportions. t-test was performed to compare the means. Odds ratio (OR) with 95% Confidence Interval (CI) was calculated to measure the different risk factor.

Multiple Logistic Regression was also performed to calculate odds ratio after adjusting confounding factors. Significance level was set at 0.05 and confidence intervals were at 95 percent level. $p \leq 0.05$ was considered statistically significant.

Results

FS are common and mostly benign. Studies have found that a simple FS is mostly benign, but prolonged febrile seizures do have long term consequences. They should be treated acutely if they continue for past 5 minutes. It is important to educate parents about the risks associated with febrile seizures.

This clinicohematological study of correlation between iron deficiency anaemia and febrile convulsion showed significant iron deficiency among cases of febrile convulsion as compared to controls considering various parameters of iron status determinents. The statistical analysis revealed the following results.

The risk of simple febrile seizure was 1.92 times more among the patients with level of ferritin<30 ng/mL as compared with the patients with level of ferritin≥30 ng/mL [OR-1.92(1.07, 3.45); p= 0.02] and the risk was significant.

The risk of simple febrile seizure was 1.76 times more among the patients with level of hemoglobin < 11 gm/dl as compared with the patients with level of hemoglobin≥11 gm/dl [OR-1.76(1.01, 3.08); p= 0.04] and the risk was significant.

Chi-square test showed that there was significant association between level of TIBC and simple febrile seizure (p=0.01). The risk of simple febrile seizure was 2.01 times more among the patients with level of TIBC>400 μg/dl as compared with the patients with level of TIBC≤400 μg/dl [OR-2.01(1.13, 3.55); p= 0.01] and the risk was significant. The risk of simple febrile seizure was 3.85 times more among the patients with level of RDW>14% as compared with the patients with level of RDW≤14% [OR-3.85(2.13, 6.97); p= 0.000006] and the risk was significant.

Therefore from above findings it can be inferred that increased incidence of febrile convulsion occurs in anaemic subjects which can be explained by the fact that, in anaemia there is deficiency of iron which is an important cofactor of brain neurotransmitters and enzymes like peroxidase , catalase and cytochromes. Iron deficiency in subjects causes behavioral and developmental abnormalities. Probably this iron deficiency in anaemic febrile children causes deficient neurotransmitter induced brain dysfunction which increases brain susceptibility to febrile seizure. Hence if iron deficiency anaemia can be prevented in children by timely determination followed by iron administration, many cases of febrile convulsion can be prevented and so also there recurrences.

Table-1: Distribution of level of hemoglobin

Level of hemoglobin (gm/dl)	Number	%
<11	141	47.0%
≥11	159	53.0%
Total	300	100.0%

Table-2: Distribution of level of ferritin

Level of ferritin (ng/mL)	Number	%

<30	109	36.5%
≥30	191	64.5%
Total	300	100.0%

Table 3: Distribution of Simple Febrile Seizures

Simple Febrile Seizures	Number	%
Present	150	50.0%
Absent	150	50.0%
Total	300	100.0%

Table 4: Level of hemoglobin and Simple Febrile Seizure

Level of hemoglobin (gm/dl)	Simple Febrile Seizure		TOTAL
	Present (n=100)	Absent (n=100)	
<11	81	60	141
Row %	57.4	42.6	100.0
Col %	54.0	40.0	47.0
≥11	69	90	159
Row %	43.4	56.6	100.0
Col %	46.0	60.0	53.0
TOTAL	150	150	300
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±s.d.	10.65±1.28	10.93±1.46	
Median	10.80	11.20	
Range	7.8-13.2	6.10-14.0	

Table 5: Level of ferritin and Simple Febrile Seizure

Level of ferritin (ng/mL)	Simple Febrile Seizure		TOTAL
	Present (n=100)	Absent (n=100)	
<30	66	43	109
Row %	60.3	39.7	100.0
Col %	44.0	29.0	36.5
≥30	84	107	191
Row %	44.1	55.9	100.0
Col %	56.0	71.0	63.5
TOTAL	150	150	300
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±s.d.	46.82±30.05	49.85±19.76	
Median	32.5	51.0	
Range	13-190	17-91	

Discussion

The relationship between iron deficiency and febrile seizures has been controversial. Most of the early and conflicting studies examined the relationship between iron deficiency and febrile seizures had small sample sizes and they used different markers and definitions for iron deficiency [11] .In this study to prove iron deficiency Hb, TIBC, Ferritin, MCV, and RDW has been taken to suggest iron deficiency.

The mean age (mean ± s.d.) of the patients was 2.18±1.22 years with range 0.56-4.83 years and the median age was 2.0 years. The proportion of the patients with age between 1-2 years (31.0%) was higher (Z=1.19; p=0.23) but it was not significant.

Test of proportion showed that proportion of males 176(58.5%) was significantly higher than that of females 124(41.5%) (Z=2.40;p=0.01). The ratio of gender was found as Male: Female = 1.4: 1.

Chi-square (χ^2) test showed that there was no significant association between age and gender of the subjects (p=0.44). The mean age (mean ± s.d.) of the males was 2.26±1.22 years with range 0.57 – 4.83 years and the median age was 2.08 years. The mean age (mean ± s.d.) of the females was 2.06±1.22 years with range 0.58 – 4.83 years and the median age was 1.75 years. t-test showed that there was no significant difference in the mean age of males and females (t_{198}=0.13;p=0.89).

47% of the subjects were having level of hemoglobin <11 gm/dl and rest 53% were having level of hemoglobin ≥11 gm/dl. The mean level of hemoglobin (mean ± s.d.) of the subjects was 10.79±1.38 gm/dl with range 6.1 – 14.0 gm/dl and the median was 11.0 gm/dl.

36.5% of the subjects were having level of ferritin <30 ng/mL and rest 63.5% were having level of ferritin ≥ 30 ng/mL.The mean level of ferritin (mean ± s.d.) of the subjects was 48.33±25.41 ng/mL with range 13.0-190.0 ng/mL and the median was 45.0 ng/mL.

Chi-square test showed that there was no significant association between gender and simple febrile seizure (p=0.88). Thus the cases and controls were matched for their gender. No significant difference of risk of simple febrile seizure was found among males as compared with females with respect to gender [OR-0.95(0.54, 1.68); p= 0.88]. Although significant male gender predominence has been seen in a study conducted by Verity C M, Butler N R, Golding J[12].

Chi-square test showed that there was significant association between level of hemoglobin and simple febrile seizure (p=0.04).The mean level of hemoglobin of cases and controls were 10.65± 1.28 gm/dl and 10.93 ±1.46 gm/dl respectively. The level of hemoglobin of the cases was significantly lower than controls. The risk of simple febrile seizure was 1.76 times more among the patients with level of hemoglobin < 11 gm/dl as compared with the patients with level of hemoglobin≥11 gm/dl [OR-1.76(1.01, 3.08); p= 0.04] and the risk

was significant although study conducted by Kulkarni S, Ghosh [13] did not find significant p value (0.07). But in a study conducted by Razieh Fallah, Behnaz Tirandazi [14] at Iran noticed significant low hemoglobin levels in cases of first attack febrile convulsion.

Chi-square test showed that there was significant association between level of ferritin and simple febrile seizure (p=0.02). The mean level of ferritin of the cases and controls were 46.82±30.05 ng/mL and 73.87±8.53 ng/mL respectively. The level of ferritin of the cases was significantly lower than that of control The risk of simple febrile seizure was 1.92 times more among the patients with level of ferritin<30 ng/mL as compared with the patients with level of ferritin≥30 ng/mL [OR-1.92(1.07, 3.45); p= 0.02] and the risk was significant. Similar significant decreased ferritin levels were also seen in cases of study conducted by Razieh Fallah, Behenaz Tirandazi [15].

After adjusting all the factors multiple logistic regression analysis showed the risk of Simple febrile seizure was 4.08 times more for RDW>14% [OR-4.08 (2.05, 8.13);p=0.0001] and the risk was significant.

In this study, the incidence of iron-deficiency anemia in the febrile convulsion group was obviously higher than the control group. Similarly, the study of Pisacane et al [16] reported that anemia in the febrile convulsion case group (30%) was higher than in the hospital control group (14%) and the healthy group (12%) . Similar positive association of febrile convulsion and iron deficiency anemia have been reported in other studies such as those carried out by Kumari *et al*. [5] Momen *et al*.[20] and Naveed Ur-Rahman and Billoo [11], Daoud A S [17] . A Kenyan case-control study as well as the meta-analysis of eight case-control studies that have examined the relationship between febrile seizures or acute seizures and iron deficiency suggested that iron deficiency may be associated with an increased risk of febrile seizures in children (Idro et al., 2010) . Fever can worsen the effects of anemia or iron deficiency on the brain, and therefore cause convulsions. But, febrile convulsion usually occurs at the onset of a febrile disease, before hemoglobin is reduced due to the infectious disease (Pisacane et al., 1996) [18]. On the other hand, some studies have reported findings that are not similar to the result of this study. For example, in the study of Hartfield et al, iron deficiency was found to be 9% and 5% in the children of two groups of febrile convulsion and febrile without convulsion, respectively; and iron-deficiency anemia was found to be 6% and 4% in the former and latter groups, respectively (Hartfield et al., 2009) [20]. Again, in the study of Kobrinsky et al [19], the febrile convulsion group suffered less from iron deficiency. They concluded that iron deficiency could have a protective effect against febrile convulsions; Bidabadi, also showed that iron deficiency in the febrile convulsion group (44%) was less than in the control group (48%), but since there was no significant difference, the protective effect of iron deficiency against febrile convulsions was not confirmed (Bidabadi et al., 2009). The major causes that lead to different results between their and our studies may be the difference in the age and number of samples, and difference in the diagnostic criteria of IDA between their and our studies. In the present study, all samples of the case group suffered from the febrile convulsion for the first time, but in most of the mentioned studies, some samples had a history of febrile convulsion. According to the findings of the present study, the incidence of iron deficiency in children suffering from fever and convulsion was observed to be more than that of fever without convulsion group. Thus, iron deficiency can be added to the list of risk factors for febrile convulsions. Accordingly, children with febrile seizures are suggested to be monitored for diagnosis and treatment of iron-deficiency anemia.

Of course, the fact that we only studied hospitalized patients could be one of the limitations of our study. Given the results of our study, it seems that iron deficiency anemia is more prevalent in febrile convulsion and probably increases the risk of convulsion.

Conclusion

The association between iron deficiency anemia and febrile seizures has been studied before numerous times but with contradictory reports. Henceforth this study has been done for further confirmation. In our study IDA was more frequently seen among children with FS than those with febrile illness alone. The result suggested that IDA may be a risk factor for first febrile seizure hence screening for IDA should be considered in children with first febrile seizure.All the investigations carried out in this study to evaluate iron deficiency anemia were found to be significantly lower in cases as compared to controls. This suggests that iron deficient children are more prone for febrile seizures and hence prophylactic iron supplementation in iron deficient anaemic children can probably avert first febrile convulsions.

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