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Original Research Article

A study of association between iron deficiency and febrile seizures

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ABSTRACT

Background: Seizure disorder is a common neurologic condition that affects 10% of kids. Febrile seizures are common in children between the ages of three months and five, with risk factors including genetics, age, gender, fever, type and duration of seizures, family and developmental history, multiple seizures, perinatal exposure to anti-retroviral medications, and pre-existing neurologic abnormalities. Risk factors include fever-induced substances, endogenous pyrogens, the cytokine network, iron deficiency, mutations associated with the Dravet syndrome, family history, high temperature, neonatal discharge, creche attendance, maternal alcohol consumption, smoking during pregnancy, and short time interval between onset of fever and first seizure.
Methods: The hospital's ethical committee granted permission to proceed, and children hospitalised for other reasons were included in the control group. Blood indices and serum ferritin were compared between case and control groups, and statistical tools were used to evaluate differences. Serum ferritin levels should be between 30 and 300 ng/ml in men and 15 to 0 ng/ml in women, and a low serum ferritin level denotes an iron insufficiency.
Results: The majority of febrile seizures were simple, with 6 (20%) having a family history. The case and control groups showed a correlation in temperature, haemoglobin levels, corpuscular volume, hemoglobin, and serum ferritin levels. Six (20%) had low serum ferritin levels of less than 30 micrograms per liter, compared to 0.03% of controls.
Conclusions: Iron deficiency is a significant risk factor for febrile seizures, with serum ferritin and red blood cell indices showing lower levels than controls.

Keywords: Iron deficiency, Febrile seizures, Risk factors, Pregnancy

INTRODUCTION

One of the most common neurologic conditions that affect children is seizure disorder. The 10% of kids in the paediatric age group experience seizures, which are common. When two or more unexplained seizures take place at a space of time larger than 24 hours apart, epilepsy is thought to be present. Epilepsy is a condition in which seizures are triggered repeatedly from within the brain. The most frequent type of childhood seizure disease, febrile seizures are uncommon before the age of six months and beyond the age of five. They are frequently inherited, and a strong family history of febrile convulsions in parents, siblings, and other close family members points to a genetic predisposition.[1,2]

Three to five percent of all children get febrile seizures throughout their first five years of life, which constitute a unique syndrome unrelated to epilepsy. In an 80 year lifespan, there is a 3.6% chance of having at least one seizure, and between 2% and 5% of neurologically healthy infants and kids have at least one. Simple febrile seizures do not raise the risk of mortality, while complicated seizures may result in a roughly 2-fold increase in mortality over the long run.[3] Simple seizures do not harm the brain and do not cause a rise in the

incidence of deviant behavior, academic performance, neurocognitive function, or attention deficits; therefore, they have no long-term negative repercussions. Febrile seizures recur in approximately 30% of those experiencing a first episode, in 50% after 2 or more episodes, and in 50% of infants <1 year old at seizure onset. Several factors affect recurrence risk.[4]

A febrile seizure is one that typically occurs in children between the ages of three months and five, is accompanied with fever, and has no known or conclusive aetiology. There are several indicators that someone will develop epilepsy after experiencing febrile seizures, including a convulsion linked to a temperature above 38 °C, the absence of any infections or inflammation of the central nervous system, the absence of any acute metabolic abnormalities that could cause convulsions, and the absence of a prior seizure history. The most prevalent micronutrient shortage in the world is iron deficiency, which is both treated and preventable. According to studies, iron affects cognition, behavior, development, and neurophysiology, and low blood ferritin levels may lower the seizure threshold.[5]

Simple (typical) and atypical febrile seizures are the two forms of febrile seizures that make up 85% and 15%, respectively, of all febrile seizures. Atypical seizures are focal, prolonged, or repeated occurrences occurring within a 24-hour period, while simple seizures are widespread, last less than 15 minutes, and do not recur during the same illness.[6] There are a number of different independent risk factors, including genetics, age, gender, fever, type and duration of seizures, family and developmental history, multiple seizures, perinatal exposure to anti-retroviral medications, history of maternal smoking and alcohol use during pregnancy, and pre-existing neurologic abnormalities. Atypical seizures may be more likely to have an underlying CNS illness, focal seizure activity, or a postictal chronic neurological impairment. Febrile seizures are common in children between the ages of six months and five years, with the majority occurring in children between 14 to 18 months of age.[7,8]

Fever-induced substances, such as interleukin-1beta, are thought to be proconvulsant in those who are vulnerable due to the stage of brain development and hereditary predisposition, which is the theory of the underlying pathophysiology. Endogenous pyrogens, which through raising neuronal excitability, may link fever and seizure activity, according to animal research. The cytokine network is activated and may have a role in the pathophysiology of febrile seizures, according to preliminary research in children. The most prevalent micronutrient shortage in the world is iron deficiency, which is both treated and preventable.[9]

The majority of patients who experienced long-lasting febrile seizures and encephalopathy following immunisation and who were thought to have had vaccine encephalopathy have mutations associated with the Dravet syndrome, proving that their condition is primary to the mutation and not secondary to the vaccine. Family history of seizures, high temperature, neonatal discharge at an older age than 28 days, creche attendance, maternal alcohol consumption and smoking during pregnancy, and a short time interval between the onset of the fever and the first seizure are all risk factors.[10]

More frequent recurrences may be linked to complex febrile convulsions and neurodevelopmental abnormalities prior to the seizures, but this effect is sporadic and modest. On the other hand, a family history of spontaneous seizures does not seem to be a significant risk factor for recurrence. Initial convulsions are more likely to happen when there is a favourable family history, and complex convulsions tend to happen at an earlier age. Complex convulsion risk is correlated with a favorable family history.[11,12]

METHODS

Place of study

The study was conducted at the Mallareddy institute of the medical sciences, multi-specialty hospital, Hyderabad.

Time of study

The study was conducted over a period 1 year from July 2015 to May 2016.

Design of study

This study is a case control hospital-based study done in the department of pediatrics, Mallareddy Hospital. Study was between August 2015 and April 2016. The study was approved by the institutional review board of Mallareddy institute of medical sciences and performed according to the ethical standards

Sample size

We enrolled children from August 2015 based on inclusion and exclusion criteria, among which 30 children were with febrile seizures and 30 were with febrile illness without seizures.

This is a hospital based prospective case control study to find the association between iron deficiency and febrile seizures in children.

Inclusion criteria

All pediatric patients with febrile seizures between age group of six months to five years presented to the pediatric department from July 2015 to May 2016 were included.

Exclusion criteria

Children with afebrile seizures, any other defined cause of seizures, child with developmental delay, child on iron therapy, children with h/o seizure disorder, children with neurological disorders / neurological deficit and children with metabolic imbalance were excluded from the study.

Methodology

The hospital's ethical committee granted the study permission to proceed. Hospital received written information about the trial. Children hospitalised for other reasons than febrile seizures were included in the control group, whereas children presenting with febrile seizures made up the case group. Parents or attendees provided written agreement for the inclusion of the kids.

For children between the ages of 6 months and 5 years who were admitted to the paediatric ward with seizures, a thorough history, general examination, and systemic examination were completed in addition to laboratory testing. Children who were hospitalised with febrile illnesses over 38 c but no serious ones and without iron supplements were divided into an age- and sex-matched control group.

Research

Calculation of serum ferritin, MCV, and MCH red blood cell indices, and haemoglobin, hemoglobin less than 11 g/dl, MCV greater than 70 fl, MCH greater than 25 pg, and serum ferritin greater than 12 micg/dl were considered iron deficient. Since serum ferritin is an acute phase reactant and its level rises under all inflammatory situations, a higher cut-off value for serum ferritin (30-60 microgram/dl) was taken into account when a fever was present. Blood indices and serum ferritin were compared between case and control groups. Hemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, and serum ferritin levels were estimated using autoanalyzers and the enhanced chemiluminescence immunoassay technique.

Statistical tools

A master chart on an excel sheet will be used to capture the data gathered for all the selected cases. With the aid of a computer and the SPSS statistical tool, version 17, data analysis will be carried out.

Measures of central tendency, measures of dispersion, the "t" value, the chi square, and the "p" values will all be computed using this software. The significance of differences between quantitative variables will be evaluated using the "t" test, and qualitative variables will be evaluated using the Yate's and Fisher's chi square tests. A significant link will be indicated by a "p" value less than 0.05.

Diagnosis

A series of biochemical and haematological processes occur in growing iron shortage. First, the bone marrow hemosiderin-represented tissue iron reserves vanish. In the absence of inflammatory disease, the level of serum ferritin, an iron storage protein, offers a rather good estimation of body iron stores. Age-dependent normal ranges and declining levels are associated with an iron deficit. Next, serum iron levels drop (also age dependant), serum transferrin levels rise, and the percentage of saturation (transferrin saturation) is below normal. Free erythrocyte protoporphyrin (FEP) builds up when the rate-limiting stage in the production of haemoglobin is the availability of iron.

The haemoglobin level drops and the red blood cells (RBC) get smaller as the insufficiency worsens. Then, the best way to identify the morphologic properties of RBCs is to measure the mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH). RBCs exhibit traits such as microcytosis, hypochromia, poilokiocytosis, and increased RBC distribution width (RDW) as the degree of deficiency increases.

Ferritin levels are sole serum indicator of storage iron, although not necessarily having a linear connection with iron reserves. S. ferritin levels should be between 30 and 300 ng/mL in men and 15 and 0 ng/ml in women.

In absence of a complicating condition, value is less than 12 g/l in iron deficiency anaemia. The serum ferritin level is often lower than 50 to 60 g/l, unless when an infectious or inflammatory condition, such as rheumatoid arthritis, is also present. The most helpful blood test for iron shortage is serum ferritin measurement, and a low serum ferritin level invariably denotes an iron insufficiency. Although bone marrow biopsy offers the most reliable assessment of body iron levels, it is difficult and uncomfortable for all people to undergo. Serum ferritin test is the most practical laboratory test to quantify iron since it correlates with total body iron reserves under steady state circumstances. Average MCV is 74 fl (range 53-93 fl), MCHC is 28 gm/dl (range 22-31 gm/dl) and MCH is 20 pg (range 14-29 pg).

RESULTS

A total of 60 youngsters were recruited for the study (n), of which 30 served as cases and 30 as controls.

Age of presentation

The children that were a part of our study ranged in age from 6 to 60 months. The mean age of controls at presentation was 22.86±12.68 months, compared to 22.56±13.78 months for cases. The proportion of each gender in the case and control groups does not differ significantly. The majority of the kids who showed up were younger than 2 years old (Figure 1). In our study,

there were somewhat more males in controls than in case group, but this difference was not statistically significant.

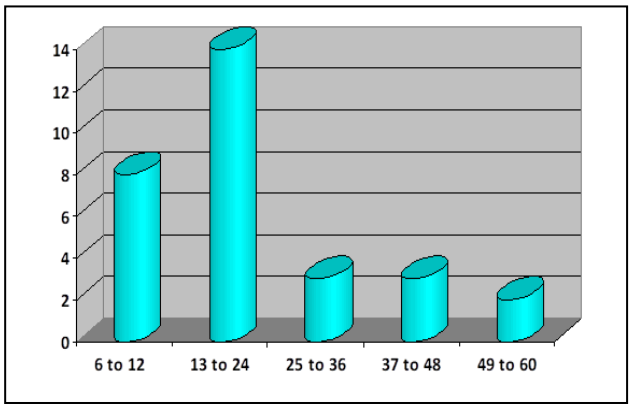

Figure 1: Age distribution among the cases in months.

Associated complaints

A thorough history of each kid was obtained in order to identify any risk factors, symptoms, or indicators that might indicate an underlying abnormality in laboratory results. In the majority of children, viral infections and respiratory tract infections were the causes of febrile illness. Twelve (40%) of the 30 children who presented to the emergency room with febrile seizures had a respiratory tract infection as the cause of their fever.

Type of febrile seizure

Of the 30 febrile seizure cases, 5 (16.3%) were complex febrile seizures and 26 (86.66%) were simple febrile seizures. Of the 30 instances of febrile seizures, 6 (20%) had a family history of febrile seizures, compared to 2 (6.6%) of the children in the control group. Therefore, in our analysis, simple febrile seizures made up the majority of febrile seizures (86.66%) while complex febrile seizures made up the minority (13.34%). The case group had a greater rate of family history of febrile seizures than the control group, suggesting that genetic susceptibility may play a role in the aetiology of febrile seizures. Three children in the case group and one in the control group have a family history of seizure disorder.

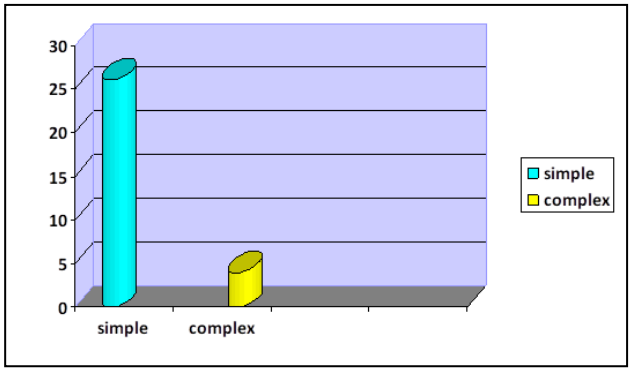

Figure 2: Type of febrile seizures in no. among cases.

Correlation of degree of temperature in case and control group

Both the case and control groups showed a correlation in the mean temperature. While the mean temperature of the control group is 101.303 SD±1.158 F, that of the case group is 101.133 SD±1.425 F. The case group's temperature is marginally higher than the control group's. T test was used to correlate the case and control groups, and the results are not statistically significant. The T value for comparing the mean temperature between the case and control groups is 0.507, and it is not statistically significant (p=0.614). T test to the compare haemoglobin levels between the case and control groups: The average haemoglobin for the case group was 10.496 SD±1.890 gm%, while it was 11.666 SD±1.270 gm% for the control group. To determine the statistical significance between the case as well as the control groups, the T test has been used.

Hemoglobin has a statistically significant T value of 2.813 (p=0.007). When compared to the control group, the haemoglobin levels in the case group were considerably lower. Of the 30 cases, 17 (56.6%) of the children had haemoglobin levels below 11 g/dl, compared to 5 (16.66%) of the children in the control group.

Comparison of mean corpuscular volume between case and control group

When compared to children without febrile seizures, children with febrile seizures have a mean MCV of 71.163 SD±6.412 fl, while children without febrile seizures have a mean MCV of 75.196 SD±5.040 fl. To determine the statistical difference between the case and control groups, the T test has been used. The statistically significant T value for mean corpuscular volume is 2.708 (p=0.009). Comparing the case group to the control group, the MCV of the case group is lower. Out of 30 cases, 15 (50%) children had a mean corpuscular volume (MCV) smaller than 70 fl, compared to 6 (20%) children in the control group.

Comparison of mean corpuscular hemoglobin between case and control group

The average corpuscular haemoglobin for the case group was 26.12 SD±2.760, while it was 27.713 SD±2.212 for the control group. To determine the statistical difference between the case and control groups, the T test has been used. The statistically significant T test for mean corpuscular haemoglobin by comparison between the case and control group is 2.441 (p=0.025). When compared to the control group, the MCH of the case group is much lower. In the 30 cases, 11 (36.6%) of the children had MCH levels below 25, compared to 4 (13.3%) of the children in the controls.

Comparison of S. ferritin between case and control group

Mean S. ferritin levels in case group=55.51 SD±18.26 micg/l, while they 68.34 SD±18.044 micg/l in control.

To determine statistical significance between the case and control groups, t test has been used. Serum ferritin t=2.737, which is statistically significant, p=0.009. When compared to control, case group's serum ferritin is much lower. A higher S. ferritin cutoff=30-60 micg/l taken into consideration because majority of kids had fevers at time of admission and because acute inflammatory conditions cause serum ferritin levels to rise. Six children (20%) out of 30 cases had very low serum ferritin levels of less than 30 micrograms/liter, compared to 0.03% of controls.

Table 1: Frequency distribution based on age and gender.

Variables	N	Age (Mean±SD) (years)	No. of males	Male %	No. of females	Female %
Cases	30	22.56±13.78	17	56.6	13	43.4
Controls	30	22.86±12.68	19	63.3	11	36.7

Table 2: Application of t test for case and control group temperatures in F.

Variables	Case	Control	Pooled	P value
N	30	30	60	0.614
Mean	101.133	101.303	101.218	
SD	1.425	1.158		
Standard error	0.260	0.211		
T test	0.507			

Table 3: Application of t test for case and control group hemoglobin (gm%).

Variables	Case	Control	Pooled	P value
N	30	30	60	0.007
Mean	10.496	11.666	11.075	
SD	1.890	1.270		
Standard error	0.345	0.231		
T test	2.813			

Table 4: Application of t test for case and control group MCV (fl).

Variables	Case	Control	Pooled	P value
N	30	30	60	0.009
Mean	71.163	75.196	73.179	
SD	6.412	5.040		
Standard error	1.170	0.920		
T test	2.708			

Table 5: Application of t test for case and control group MCH (pg).

Variables	Case	Control	Pooled	P value
N	30	30	60	0.025
Mean	26.12	27.713	26.916	
SD	2.760	2.212		
Standard error	0.504	0.404		
T test	2.441			

Table 6: Application of t test for case and control group serum ferritin (micg/l).

Variables	Case	Control	Pooled	P value
N	30	30	60	0.009
Mean	55.51	68.34	61.925	
SD	18.26	18.044		
Standard error	3.334	3.294		
T test	2.737			

Table 7: Hematological parameters of cases and controls.

Variables	Cases±Std error	Controls±Std error	T test	Probability
Temperatur (F)	101.1333±0.26021	101.3033±0.2115	0.507	0.614
Haemoglobin (gm%)	10.4967±0.3451	11.6667±0.2319	2.813	0.007
MCV (fl)	71.1633±1.1708	75.1967±0.9202	2.708	0.009
MCH (pg)	26.1233±0.5039	27.713±0.4038	2.4415	0.025
Sr. ferritin (mcg/l)	55.51±3.3339	68.345±3.2945	2.7373	0.009

DISCUSSION

Febrile convulsions are the most frequently occurring epilepsy syndrome (3-4%) in children between 6 months and 5 years of age 1, but the incidence is as high as 15 percent in some populations. This incidence has been attributed to closer living arrangements among family members making detection more likely, but racial and geographic variations may also be important.[13]

In our study majority of cases are males (56.6%). This is in concurrence with general trend of febrile seizures. In our study most of the children presented were below 2 years. The risk of complex febrile convulsion increases if first fit occurs at a younger age. In our study 4 children had complex febrile seizures and out of them 2 occurred below 1 year. Al-Eissa et al and Farwell et al have also reported that age less than 12 months was related with increased incidence of complex febrile convulsions.[14]

Both the case and control group were age and sex matched, so there is not much of difference to avoid age and gender bias. The mean age of case group is 22.56 SD±13.78 months and the mean age of controls was 22.86 SD±12.68 months. The percentage of males in case group is 56.6% and the percentage of males in control group is 63.3%. So, there is not much of difference and is not statistically significant.[15,16]

In our study, majority of children had high grade fever at the presentation. The mean temperature of cases was 101.133 SD±1.425 F and the mean temperature of children without febrile seizures was 101.303 SD±1.158 F. There is no difference between the peak temperature of case and control group. In fact, the mean temperature of children without febrile seizures was slightly higher than the children with febrile seizure. The finding argues against high fevers as a factor contributing to the severity of a seizure.[17]

The most common cause of fever in our study leading to febrile convulsions was upper respiratory tract infections (36.66%). Rantala et al 45 in 1995 has also reported in their study that upper respiratory tract infection was the most common cause of fever in febrile convulsions.

A positive family history of febrile seizures points to the importance of genetic factors and common environmental exposures. In our study 6 (20%) children had positive family history of febrile convulsions. Saidulhaque in 1981, 55 has reported 20% of children with positive family history in his study. Thus, the genetic contribution to incidence of febrile seizures is manifested by a positive family history for febrile seizures. In many families the disorder is inherited as an autosomal dominant trait, and multiple single genes causing the disorder have been identified. In most cases the disorder appears polygenic, and the genes predisposing to it remain to be identified.[16]

In our study, most of the children (86.66%) had simple febrile seizures. Around 4 (13.34%) children came with complex febrile seizures. Among the children presenting with complex febrile seizures, 2 children were less than 1 year of age suggesting that the incidence of complex febrile seizures is higher among the children presenting in less than 1 year of age.

Iron deficieny was defined as hemoglobin less than 11 g/dl, MCV<70 fl, MCH<25 pg serum ferritin <12 micg/dl. Since serum ferritin is acute phase reactant and its level is increased in any inflammatory conditions, in presence of fever a higher cut-off value of serum ferritin (30-60 microgram/dl) was considered. Case and controls were compared with respect to blood indices and serum ferritin. Estimation of hemoglobin, mean corpuscular volume, mean corpuscular haemoglobin by auto analysers and serum ferritin level by Enhanced chemiluminescence immunoassay method is done.[17,19]

On laboratory investigation the mean hemoglobin for case group is 10.496 SD±1.890 gm% and the mean hemoglobin for the control group is 11.666 SD±1.270 gm%. Out of 30 cases 17 (56.66%) children had hemoglobin less than 11 gm% whereas 5 (16.66%) children in control group had hemoglobin less than 11 gm%. T test for hemoglobin is 2.813 and is statistically significant (p=0.007). The hemoglobin levels were significantly lower in case group compared to control group.

The mean MCV of children with febrile seizures is 71.163 SD±6.412 fl and the mean MCV in children without febrile seizures is 75.196 SD±5.040 fl. The MCV of case group is lower when compared to control group. Out of 30 cases 15 (50%) children had Mean corpuscular volume less than 70 fl whereas 6 (20%) children in control group had MCV less than 70 fl. T value for Mean corpuscular volume is 2.708 and is statistically significant (p=0.009).[20]

The mean corpuscular hemoglobin of case group is 26.12 SD±2.760 and the Mean corpuscular hemoglobin of the

control group is 27.713 SD±2.212. Out of 30 cases 11 (36.6%) children had MCH less than 25 pg where as in controls 4 (13.3%) children had MCH less than 25 pg. T test for Mean corpuscular hemoglobin by comparison between the case and control group is 2.441 and is statistically significant (p=0.025). The MCH is of case group is significantly lower when compared to the control group.

Among all the above investigations, serum ferritin is more specific for iron deficiency. Since serum ferritin level increases in acute inflammatory settings and as most of the children in our study presented with high fever initially, a higher cut off value was considered (30-60 µg/l). A low serum ferritin less than 30 µg/l is almost definitive of iron deficiency.

The mean serum ferritin of the case group is 55.51 SD±18.26 µg/l and the mean serum ferritin of the control group is 68.34 SD±18.04 µg/l. The serum ferritin of case group is significantly lower when compared to the control group. Out of 30 cases, 6 children (20 %) had very low serum ferritin <30 µg/l where as in controls 1 (0.03%) children had serum ferritin less than 30 µg/l. T test value for serum ferritin is 2.737 and is statistically significant. p=0.009.

So as per our study there was definite association between iron deficiency and febrile seizures. The incidence of iron deficiency was significantly higher in the case group when compared to the control group. The levels of all the hematological parameters considered for diagnosing iron deficiency were significantly lower in the case group when compared to the control group.

Leela Kumari et al did a case control study which was similar to our study.[21] A case control study was done in the department of pediatrics, SAT hospital, Thiruvananthapuram during August 2009 to February 2010. The 154 cases and 154 controls were included in the study. Cases were children of age group 6 months to 3 years presenting with simple febrile seizures to the pediatric emergency department and wards of the hospital during the study period. The study concluded that iron deficiency is a significant and modifiable risk factor for simple febrile seizures in children of age group 6 months to 3 years. As in our study this study also postulates that iron deficiency is a significant risk factor for simple febrile seizures. Early detection and timely correction of iron deficiency may be helpful for prevention of simple febrile seizure in children of this age group.

Pisacane et al did a case control study on 156 children aged 6-24 months admitted to Castellammare di Stabia Hospital, Naples, between 1st January 1993 to 30th June 1995 with diagnosis of febrile convulsions.[22] They were healthy children without previous afebrile seizures or central nervous system disease. Finally, they concluded the study with the comment that low iron level is associated with febrile seizures and alternatively anemia can be associated with the severity of a febrile illness. In our study it has been found that more percentage of children with simple febrile seizures have low Hb and Sr. ferritin levels, indicating an association between low iron levels and febrile seizures as in above study.[23]

The main advantage of our study compared to the above studies is that we considered a higher cut off value for serum ferritin considering its rise in acute inflammatory settings.

Vaswani et al conducted study among 100 children, dividing equally children between 6 months and 6 years with first febrile seizure as cases and febrile illness without seizure as controls.[17] The results of this study showed the proportion of children with low ferritin (<25 µg/l) was significantly higher in cases (34.68%) than in controls (15.30%) with value of <0.0001. the concluded that iron deficiency could be a potential risk factor for febrile seizure in children. The results of this study were also similar to our study underlying the importance of iron deficiency in children with febrile seizures.[24-26]

So, as per our data we find iron deficiency as a risk factor for febrile seizures and there is significant association between iron deficiency and febrile seizures.

Our study was done at a referral center; hence we could not extrapolate the result of our study to general population trend. However, with our study findings we strongly recommend that further larger studies are required and other measures of iron sufficiency including plasma ferritin should be measured to confirm the findings in our study.

CONCLUSION

According to this study, febrile seizures are more common in men than in women, peak in frequency before age 2, and become more complicated before age 1. 20% of children had a positive family history of febrile seizures, which have a hereditary tendency. Additionally, iron deficit was discovered to be a risk factor, with serum ferritin and red blood cell indices showing considerably lower levels of iron deficiency than controls. This shows that a significant risk factor for febrile seizures is iron deficiency.

Recommendations

With a complete nutritional history and CBC, iron deficiency should be thoroughly checked for as it is a risk factor for febrile convulsion. Treatment for iron deficiency may reduce the likelihood of seizure recurrence and stop other side effects. The results need to be confirmed by another research.

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