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Original Research Article

The association between iron deficiency anemia and febrile seizures

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ABSTRACT

Background: Febrile seizures are seizures that occur in children between 6 months and 60 months of age , with body temperature of 38ºC or higher not resulting from Central Nervous System (CNS) infection or any metabolic imbalance without any prior afebrile seizures. Among many risk factors identified for febrile seizures, iron deficiency is hypothesized to be one of the risk factor for occurrence of febrile seizures.
Methods: A total of 100 children aged between 6 months to 5 years were included in the present study and were further divided into 2 groups of 50 each, as cases and controls. Control group consisted of age and gender matched children admitted with acute febrile illness without seizures. A detailed history was taken and clinical examination was done in both cases and controls with particular attention to development delay and family history of seizure. Complete haemogram, iron profile and other appropriate investigations were done in both the groups and results were compared.
Results: The mean age of onset of febrile seizures was 32 months. There was slightly male predominance, with male: female ratio of 1.27:1. Majority of children with febrile seizures were found to have iron deficiency anemia as opposed to children in control group which was statistically significant. (76% vs 28%), p-value<0.001. All the indices of iron deficiency anemia, like haemoglobin, MCV, MCH, serum iron, serum ferritin were low in febrile seizures group compared to control group. The difference was found to be statistically significant (p-value<0.001).
Conclusions: Iron deficiency anemia (IDA) was more frequent among children with febrile seizures. The result suggests that IDA may be a risk factor for febrile seizures. Early detection and timely correction of iron deficiency may be of help for prevention of recurrence of febrile seizures in children of this age group.

Keywords: Febrile seizures, Hemoglobin, IDA-iron deficiency anemia

INTRODUCTION

Febrile seizures (FS) are seizures that occur in children between the ages of 6 months and 60 months, with body temperature of 38ºC or higher not resulting from Central Nervous System (CNS) infection or any metabolic imbalance without any prior afebrile seizures. This condition occurs in 2-5% of the children who are neurologicallyhealthy.[1] A simple febrile seizure is a primary generalized, usually tonic-clonic attack associated with fever, not recurrent within a 24-hour period and lasting for a maximum of 15 min. A complex febrile seizure is more prolonged (>15 min), is focal, and /or reoccurs within 24 hour.[1] The precise cause of febrile seizure is not known, but several genetic and environmental factors have been implicated.[2] The maximum age of febrile seizure occurrence is 14-18 months, which overlaps with the maximum prevalence of Iron Deficiency Anaemia (IDA).[3] IDA is the most common nutritional deficiency in the world. Iron is an important micronutrient which is used by roughly all the cells in the human body. Iron is used as cofactor for metabolism of many neurotransmitters, monoamine and aldehyde oxidase in the brain. The metabolism of these neurotransmitters, monoamine and aldehyde oxidase will be affected in the patient with iron deficiency leading to

decrease in these neurotransmitters, which may decrease the threshold for seizure. Fever can worsen the negative effects of low serum ferritin on the brain and trigger seizure.[4]

Different factors have been considered for febrile seizures, including familial (genetic) factors, prenatal factors, present acute illness, the highest degree of fever and finally anemia. Iron deficiency anemia (IDA), as the most common type of anemia during infancy and childhood, occurs usually between 9-24 months of age and this period coincides with the peak incidence of FS. It has been determined that iron depletion has negative effect on neurocognitive functions of children and supplemental iron can reduce breath holding spells. On the other hand, fever can exaggerate the negative effect of anemia on brain.[5]

Considering the age of prevalence of IDA and FS which are the same, the role of iron in the metabolism of neurotransmitter (such as GABA and serotonin) and some enzymes (such as monoaminoxidase and aldehydase), a relationship between IDA and FS is probable. With respect to the high prevalence of febrile seizures and IDA in children and considering the fact that IDA is a probable risk factor for febrile seizure occurrence, this study was conducted to determine the association between iron deficiency anemia and febrile seizure.

METHODS

The study was a hospital based case control study which was conducted at ESIC MC and PGIMSR hospital, Bengaluru, Karnataka, India, from January 2018 to June 2019. A total of 50 Children in the age group from 6 months to 5 years admitted with first episode of simple febrile seizure were taken as cases. The control group included 50 children in the same age group admitted with acute febrile illness without seizures. Children with epilepsy and developmental delay were excluded from the study. Children on iron therapy were also excluded.

A detailed history was taken in cases regarding duration of fever, time interval between onset of fever and convulsion, duration for which convulsion lasted, history of developmental delay and family history of epilepsy. Detailed examination was done in cases to rule out possible central nervous system infection, developmental delay and any other co-morbidities. Control group was also examined to rule out any associated significant co-morbidities.

Complete haemogram, red cell indices, iron profile were done in both the groups. Other necessary investigations were carried out wherever it was necessary. Diagnosis of iron deficiency anemia was made in a child with low haemoglobin (<11gm/dl), peripheral smear findings of microcytic hypochromic anemia with reduced RBC count and increased red cell distribution width (RDW>15%).

The sample size was calculated considered the level of significance of 5% (type 1 error) and power of study as at least 80%. Data was analysed using appropriate descriptive and inferential statistics. The categorical type data was expressed in terms of frequencies and percentages whereas the numeric continuous data as mean±SD. All the bio-chemical markers were expressed as mean±SD. In order to compare the various markers in two groups, independent student's t-test was used. Odd ratio was calculated as a risk of iron level in cases with seizures to the group without seizures along with 95% CI. For all statistical evaluations, a p-value<0.05 was considered as statistically significant. Qualitative data was summarized using charts and diagrams. Data was analysed using statistical package SPSS-20.

RESULTS

The study group consisted of total 100 children. Among them, 50 were cases and 50 controls. Majority of the children were in age group of 36-60 months in both the groups. (40% in cases, 36% in controls). The mean age group of children with febrile seizure was 32 months.

Majority of children were males (56% and 54% in case and control group respectively). Male to female ratio was 1.27:1 among cases. Majority of children belonged to lower socioeconomic class in both the study groups. (80%, 60% among cases and controls respectively). Majority of children in both the groups were exclusively breastfed (80% and 70% in cases and control respectively). Initiation of complementary feeding at 6 months of age was poor in children with febrile seizure group compared to controls (20% versus 50%).

Mean Hb level among cases was 7.5g/dl whereas in controls it was 12.64g/dl, which was statistically significant (p-value<0.001). Mean MCV and MCH levels in the cases were 62.5fl, 22.04pg and in controls, these values were 75.88fl, 30.34pg, respectively which was statistically significant. Mean RDW among cases was 15.08% compared to controls (12.22%) which was statistically significant.

Mean serum iron level was found to be low among cases compared to controls (44.46 mg/dl and 120.4mg/dl respectively). Mean TIBC was 478.5 microgram/dl in cases and 301.8 mcg/dl in control, which was statistically significant (p value<0.001).

Transferrin saturation was less among case group (12.08%) compared to controls (39%), the difference was statistically significant. Mean serum ferritin level was 20.50 mcg/l in the cases and 71.65 mcg/l in controls which was statistically significant (Table 1).

Table 1: Red cell indices and iron profile among study group.

Lab parameters	Cases (n=50)		Control (n=50)		P- value
	Mean	SD	Mean	SD	
Hemoglobin (gm/dl)	7.54	1.10	12.64	1.71	<0.001
MCV(fl)	62.5	4.38	75.88	4.29	<0.001
MCH (pg)	22.04	2.50	30.34	2.48	<0.001
RDW%	15.08	1.22	12.22	1.06	<0.001
TIBC (mcg/dl)	478.5	44.43	301.80	48.01	<0.001
S.Iron (mcg/dl))	44.46	2.67	120.54	29.08	<0.001
S.Transferrin (mg/dl))	277.04	29.54	269.20	43.18	0.2919
Transferrin saturation (%)	12.08	1.41	39.00	13.89	<0.001
Serum ferritin (microgram per litre)	20.50	1.07	71.65	5.4	<0.001

Iron deficiency anemia was found in 38 children in the case group (76%) and 14(28%) in control group.

DISCUSSION

The mean age of onset of febrile seizure in the present study was 32±12 months which was comparable to other studies. Similar observation was made in a study done by Amir et al (39±15.92 months). However lower age group of onset of febrile seizures was observed in study done by Alfredo et al ,Vasvani et al, Waruiru et al, Azhar et al, Naveed et al and Ellenberg et al.[8-12] Mean age for first febrile seizure was found to be 20.76±11 months.

There was a preponderance of males in the febrile seizures group in the present study with male to female ratio (1.27:1). Similar findings were observed in studies done by Kumari et al, Hartfield et al, Azhar et al and Alberto et al.[13,14] Regardless of the era of the study or particulars of the design; boys have consistently emerged with higher frequency of febrile seizures. Incidence ratios of boys: girls have ranged from 1.1:1 to 2:1.

In the present study mean hemoglobin level was 7.54gm/dl which was significantly low as compared to controls (7.54 gm/dl vs 12.64 gm/dl), p value<0.0001. Kumari et al, Naveed et al and Piscane et al have reported similar results while Khalid et al failed to find any significant difference between the two groups. In the present study the mean MCV was found to be low among the cases compared to the controls (62.5fl vs 75.88fl) which was statistically significant. Similar findings were observed in studies done by Kobinsky et al, Pisacane et al, Naveed-ur-Rehman et al, Amir salari et al and Kumari et al.[15] The mean MCH among the case group was low compared to the controls (22.02pg and 30.34pg respectively) and the result was statistically significant. Studies done by Kobrinsky et al, Daoud et al and Naveed-ur et al also observed similar findings. In the present study, the red cell distribution width (RDW) in cases was 15.02% where as in controls it was 12.22%. The difference of red cell distribution width among cases and controls was statistically significant.

In the present study the mean serum iron levels in cases and controls was 44.46 mgl/dl and 120.4 mg/dl respectively. The mean serum iron level difference was statistically significant. Pisacane et al studied the serum iron level among febrile seizure group and they also found it to be statistically significant. The total iron binding capacity in case and control group were 478.5 and 301.8 respectively. The present study results were in accordance with the study conducted by Khalid et al. who found the TIBC of 438-575 micro gram /dl.

The mean serum ferritin was found to be low among cases as compared to controls (20.50 microgram/l vs 71.65microgram/l) and the difference was statistically significant. Similar results were observed in study done by Kobrinsky et al, Pisacane et al, Naveed et al. Kumari P L et al, Azhar s et al (Table 2).

Table 2: Comparison of various laboratory parameters among different studies (mean values).

Study	Hb (gm/dl)	MCV (fl)	MCH (pg)	Serum iron (mcg/dl)	Serum ferritin (mcg/l)
Present study	7.54	62.5	22.04	44.46	20.5
Kumari PL et al	9.4	67	24.8	45.67	29.5
Pisacan et al	10.5	70	25.3	42.10	15.5
Naveed-ur-rehman et al	10	70	24	40	22
Kobinsky NL et al	10.2	72	24	45.6	20
Vaswani RK et al	9.4	73.4	21.4	50.2	31.9

CONCLUSION

Iron deficiency anemia was more frequent among children with febrile seizure. Strong association was found between various parameters of iron deficiency anemia and occurrence of febrile seizure. The result suggests that IDA may be a risk factor for febrile seizure. Screening for IDA should be considered in children with febrile seizure. Early detection and timely correction of iron deficiency may be of help for prevention of recurrence of febrile seizures in children of this age group.

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