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Original Research Article

A Hospital-Based Assessment of Iron Deficiency Anemia as a Risk Factor for First Febrile Seizures: Case Control Study

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Abstract

Aim: To determine the association between Iron Deficiency Anemia (IDA) and the first episode of febrile seizures (FFS).

Methodology: This research would be a Prospective case-control study for both children with the first episode of febrile seizures and febrile illness in the Department of Pediatrics, DMCH, Darbhanga, Bihar for 10 months (November 2021 to August 2022). This study includes two groups. Cases includes 50 consecutive children admitted in pediatrics ward fulfilling the following criteria. Control Group features 50 infants from 6 months to 5 years who have the febrile illness without convulsions. After obtaining informed consent from the parents of children to be enrolled for the study relevant history, examination and laboratory investigations were collected in a predesigned proforma. Investigation like hemoglobin, blood indices (MCV, MCH), and serum iron and serum ferritin are done for detection of iron deficiency anaemia and their relationship with the first episode of febrile seizure was observed.

Results: In our study comprising 50 cases and 50 controls, 54% of cases were diagnosed as IDA with FS, 20% of controls were diagnosed as IDA. This suggests IDA as a risk factor for febrile seizures with a significant P value of <0.001. The average Hb value in cases was 9.02±1.56 and control values were 9.92±1.29, a mean MCV value of 66.94±15.21, control value of 84.42±14.22, and a mean MCH value of 31.14±13.98 in cases and control values of 37.04±9.62. The mean Serum Ferritin level was 46.21±65.78 in our sample of 50 cases, whereas the mean Serum Ferritin level was 55.21±24.42 in controls. The average serum iron level in our sample was 77.02±45.12, and the average serum iron level in our controls was 97.42±38.78. The mean level of TIBC for this analysis in cases was 435.16±123.85 and the mean level of TIBC in controls was 349.46±101.02. Throughout this analysis, the average level of Serum Transferrin in this sample was 245.62±62.24, and the mean amount in the controls was 292.24±50.12.

Conclusion: Iron deficiency anaemia is a significant risk factor in lowering the seizure threshold for FS children between the age group of 6 months to 5 years. IDA was more frequent in children with Febrile Seizures than children with febrile illness alone. The findings indicate that IDA may be a risk factor for FFS. IDA monitoring should be done in children with FFS.

Keywords: Iron Deficiency Anaemia, Seizures, Febrile Illness.

Introduction

Febrile Seizures (FS) is the most common convulsive disorder of children and occurs in 2-5% of the overall number of children (or 4.8/1000) were impacted per year [1]. Febrile Seizure was classified as fever-related seizures. The disorder presents with a fever of 38◦C in children from 6 months to 5 years old and does not include signs of central nervous system disorders or any other potential triggers [1]. Trigger factors for this condition include a family history of convulsion or FS, brain injury, mothers who consume or drink alcoholic drinks and high fever [2–6].

Iron deficiency is the commonest micronutrient deficiency worldwide, and is a preventable and treatable condition [7]. Iron plays an important role in brain energy metabolism [8, 9], myelin formation and neurotransmitter metabolism [10-13]. Iron deficiency affects the regional monoamine metabolism, such as serotonin, dopamine and norepinephrine, glutamate and gamma-aminobutyric acid (GABA) [14-17].The fetal brain may be at risk even if the infant is not anemic, because when there is not enough iron supply, the first priority of iron is red blood cells instead of other tissues [18]. Thus, iron deficiency may alter the seizure threshold of a child [19, 20]. Iron deficiency is postulated as a risk factor for febrile seizures in children and it is an easily correctable condition [21, 22].

The WHO 1995–2011 global anaemia report states that nearly 43% of babies, 38% of pregnant women, and 29% of non-pregnant women and 29% of all reproductive-age people worldwide suffered from anaemia, equal to 273 million young teenagers, 496 million non-pregnant, and 32 million pregnant women [7]. Anemia (IDA) is one of the world's most severe issues in the diet. 46-66 percent of those below five are anaemic within developing nations. 58.5 percent of under-5are anemic in India, according to NFHS-4 [23].

The relationship between iron deficiency anemia (IDA) and FS has been evaluated in several studies with conflicting results. The aim of this case-control study was to evaluate the relation of Iron Deficiency Anemia with the first episode of Febrile Seizure. A family history of convulsions; maternal smoking; and alcohol consumption during pregnancy have been associated with febrile seizures, but the risk factors remain largely unknown. Iron is involved in the metabolism of several neurotransmitters, and monoamine and aldehyde oxidase are reduced in iron deficiency anemia, which is common during the second and the third year of life and has been associated with behavioral and develop mental disturbances. We, therefore determined the association between Iron Deficiency Anemia (IDA) and the first episode of febrile seizures (FFS).

Methodology

This research would be a Prospective case-control study for both children with the first episode of febrile seizures and febrile illness in the Department of Pediatrics, DMCH, Darbhanga, Bihar for 10 months (November 2021 to August 2022). This study includes two groups. Cases includes 50 consecutive children admitted in pediatrics ward fulfilling the following criteria. Control Group features 50 infants from 6 months to 5 years who have the febrile illness without convulsions. After obtaining informed consent from the parents of children to be enrolled for the study relevant history, examination and

laboratory investigations were collected in a predesigned proforma.

Inclusion Criteria: Children with first simple febrile seizure between 6 months and 5 years.

Exclusion Criteria: Children aged < 6 months and > 5years, children presenting with atypical febrile seizures, children presenting with afebrile seizures or those having any signs of CNS infection or metabolic seizures, children with a history of birth asphyxia/ developmental delay, children on Iron supplementation therapy, very sick children, children who fall into the Grade IV PEM category on IAP charts, and/or children with family h/o Epilepsy/ mental retardation.

Demographic data, seizure details, nature of the febrile illness, family history of epilepsy/ febrile seizures were recorded. The vitals of the child (HR, RR, peripheral pulses, blood pressure, and temperature) were recorded. General physical examination and nutritional status according to IAP weight for age classification were used to grade protein-energy malnutrition. Systemic examination was done as per the proforma. The following investigations were done in all cases and controls at the time of admission:

1. Hemoglobin, blood indices (MCV, MCH, MCHC).
2. Blood glucose: Random blood sugar was with glucometer and then confirmed by glucose oxidase peroxidase method.
3. Serum electrolytes (S. Sodium, S. Potassium and S. Chloride).
4. S. Calcium.
5. Iron studies (S. Iron, S. Ferritin, and TIBC).

All the patients were treated according to the diagnosis. An investigation like hemoglobin, blood indices (MCV, MCH), serum iron and serum ferritin done for detection of iron deficiency anemia and their relationship with febrile seizure was observed. Methods and diagnostic criteria for iron deficiency anaemia used in present study are as follows [12]: Hemoglobin < 11g/dl, MCV <70 fl, MCH <27 pg, and Serum ferritin <12 microgram/dl. Statistical Analysis Data analyses were done using SPSS 20.0.

Results

Among 50 cases 34% cases were < 1 year, 28% cases were 1-2 years, 20% cases were 2-3 years, 10% cases were 3-4 years and 8% cases were > 4 years. Among 50 controls, 48% controls were < 1 year, 14% controls were 1-2 years, 22% controls were 2-3 years, 12% controls were 3-4 years and 4% controls were > 4 years. In our study among 50 cases, 60% were males while 40% were females. Among controls, 62% were males and 38% were females. The mean age of cases was 2.30+1.45 years and the mean age among the control group was 1.92±1.78 years.

Table 1: Demographic Data for Age and Gender Distribution for both Case and Controls

Age in years	Cases		Controls	
	N	%	N	%
<1 year	17	34.0	24	48.0
1-2 year	14	28.0	7	14.0
2-3 years	10	20.0	11	22.0
3-4 years	5	10.0	6	12.0
4-5 years	4	8.0	2	4.0
Total	50	100.0	50	100.0
Mean ± SD	2.30±1.45 years		1.92±1.78 years	
Gender				

Male	30	60.0	31	62.0
Female	20	40.0	19	38.0
Total	50	100	50	100

The average weight was 9.72±2.56 Kgs and 8.78±2.32 Kgs. In the present study out of 50 cases, 100% were of lower SES. Among 50 controls 92% of controls were of lower SES and 8% of controls were of middle SES. In the present study out of 50 cases of the first episode of simple febrile seizures 72% cases of seizures lasted for < 5 minutes and 28% cases of seizures lasted for 5-10 minutes. In our study among 50 cases of the first episode of simple febrile seizures 94% cases had up rolling of eyes and 30% of cases had a deviation of angle of mouth. In the present study among 50 cases and 50 controls 10% cases had a positive family history and 2% controls had a positive family history.

Table 2: Weight, Socio-Economic Status, Average Duration of Seizures, Comparison of Other Parameters, Family History of Febrile Seizures in Study Group

Weight (kg)	Cases (n=50)	Controls (n=50)
<10 kg	35(70.0%)	44(88.0%)
>10 kg	15(30.0%)	6(12.0%)
Mean ± SD	9.72±2.56	8.78±2.32
Socio-economic status		
Lower	50(100.0%)	46(92.0%)
Middle	0	4(8.0%)
Upper	0	0
The average duration of seizures		
<5 min	36(72.0%)	0
5-10 min	14(28.0%)	0
>10 mins	0	0
Other parameters		
Uprolling of eyes	47(94.0%)	0(0%)
Deviation of the angle of mouth	15(30.0%)	0(0%)
Family history		
Yes	5 (10.0%)	1 (2%)
No	45 (90.0%)	49 (98%)

Table 3: Mean Values of Various Blood Parameters

Parameters	Cases	Controls	P-value
Hemoglobin	9.02±1.56	9.92±1.29	P<0.001
MCV	66.94±15.21	84.42±14.22	P<0.001
MCH	31.14±13.98	37.04±9.62	P=0.005
Serum ferritin	46.21±65.78	55.21±24.42	P=<0.03
Serum Iron	77.02±45.12	97.42±38.78	P=0.037
T1BC	435.16±123.85	349.46±101.02	P<0.001
Serum Transferrin	245.62±62.24	292.24±50.12	P<0.001

In the current analysis, the average Hb value in cases was 9.02±1.56 and control values were 9.92±1.29, a mean MCV value of 66.94±15.21, control value of 84.42±14.22, and a mean MCH value of 31.14±13.98 in cases and control values of 37.04±9.62. The mean Serum Ferritin level was 46.21±65.78 in our sample of 50 cases, whereas the mean Serum Ferritin level was 55.21±24.42 in controls. The

average serum iron level in our sample was 77.02±45.12, and the average serum iron level in our controls was 97.42±38.78. The mean level of TIBC for this analysis in cases was 435.16±123.85 and the mean level of TIBC in controls was 349.46±101.02. Throughout this analysis, the average level of Serum Transferrin in this sample was 245.62±62.24, and the mean amount in the controls was 292.24±50.12.

Table 4: Diagnosis

Diagnosis	Cases (n=50)	Controls (n=50)	P-value
IDA	27 (54.0%)	10 (20%)	<0.001
FS	23(46.0%)	0	
Others	0	40(80%)	

In our study comprising 50 cases and 50 controls, 54% of cases were diagnosed as IDA with FS, 20% of controls were diagnosed as IDA. This suggests IDA as a risk factor for febrile seizures with a significant P value of <0.001.

Discussion

Iron deficiency was found as a significant risk factor for simple febrile seizures in children of age group 6 months to 5 years in our study. In the study done by Pisacane, et al. [24], among children of the same age group, similar results were noted and the odds ratio was 3.3 (95% CI of 1.7-6.5). Iron status was measured by hemoglobin, MCV and serum iron in that study. Dawn, et al. [25] also found similar results with children with febrile seizures almost twice likely to have iron deficiency compared to controls.

In the study by Daoud, et al. [26], the significance of iron status as a possible risk factor was evaluated. The mean serum ferritin level in the cases was 29.5 mcg/L, much lower than the values in the controls (53.5 mcg/L). Similar observations were made in a study done by Vaswani, et al. [27] from Mumbai. The mean serum ferritin level was significantly low in children with first febrile seizures (31.9±31.0 mcg/L) as compared to controls (53.9±56.5 mcg/L) (P=0.003). However, no significant difference was noted in the mean hemoglobin value of cases (9.4±1.2 g/dL) and controls (9.5±1.0 g/dL) (P=0.7), or in the mean value of blood indices.

Kobrinsky et al [28] and Abbaskhanian et al [29] found a higher level of iron deficiency anemia in the control groups and concluded that anemia raises the threshold for febrile seizure and iron deficiency may protect against the development of febrile convulsions. The results of this study demonstrated the significantly higher frequency of iron deficiency in patients with febrile seizure. The same results are shown by Hartfield et al [30], Daoud et al [26] and Vaswani et al [27], but the results by Bidabadi et al [31], Salehi et al [32], and Amirsalari et al [33] are different.

Daoud et al [26] observed a significantly lower ferritin level in the first febrile seizures group than in the reference group proving that serum ferritin is a sensitive, specific and reliable measurement for determining iron deficiency at an early stage, and it may be the best indicator of total body iron status. Vasvani et al [27] observed significant low serum ferritin levels in children with FFS than in controls. On the contrary, few studies [31, 33] found no significant difference in serum ferritn level between the two groups.

Our study had an mean Hb of 9.02±1.56 g/dl and 9.92±1.29 g/dl in case and control respectively with a p value of <0.001 which is similar to study conducted by Pisacane A et al [24] with a mean Hb of 10

g/dl and 12.5 g/dl in case and control respectively (p value of 0.0001) , Taee N et al [34] had an mean Hb of 11.55 ±1.34 g/dl and 12.2 ±1.5 in case an control respectively with a p value of 0.01 , Aly I et al [35] had mean Hb of 8.1±1 g/dl and 11.1±1.8 in case and control respectively with a p value of 0.001. Few have obtained contrast results of no statistically significant difference in Hb in cases and controls [26, 31, 36].

Our study group had a mean Serum Ferritin (SF) of 46.21±65.78 and 55.21±24.42 in case and control respectively with a p value of 0.001. Similar results have been obtained in various similar case control studies [34-36]. S. ferritin being an acute phase reactant, low levels in the setting of fever makes it a more reliable indicator. Although RDW is an indicator of iron status our study did not have significant difference in RDW in cases and controls. [37]

Conclusion

Iron deficiency anaemia is a significant risk factor in lowering the seizure threshold for FS children between the age group of 6 months to 5 years. IDA was more frequent in children with Febrile Seizures than children with febrile illness alone. The findings indicate that IDA may be a risk factor for FFS.IDA monitoring should be done in children with FFS.

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