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ASSOCIATION BETWEEN IRON DEFICIENCY ANEMIA AND FEBRILE SEIZURES IN CHILDREN

Dr Pooja B Amble Postgraduate resident, Department of Pediatrics, GMC, Bhopal

Dr Rashmi Randa* Associate Professor, Department of Pediatrics, GMC, Bhopal*Corresponding Author

Dr Jyotsana Shrivastava Professor and Head of Department, Department of Pediatrics, GMC, Bhopal

ABSTRACT **Background:** Febrile seizure is one of the common neurologic problem in children, occurring in 2-5% of children. Iron deficiency anemia is postulated as a risk factor for febrile seizures in children and it is easily preventable and treatable disease. This study was done to evaluate association between iron deficiency anemia and febrile seizures in children of age group 6 months to 60 months. **Methods:** This observational case control study was conducted at a tertiary care hospital in central India. This study included 60 consecutive cases and 30 concurrent controls. All children of age group 6-60 months admitted during study period of one year with febrile seizures were enrolled as cases(n=60). During the same duration, children of same age group admitted with febrile illness without seizures were enrolled as controls (n=30). Blood investigations including hemoglobin, red blood cell indices and serum ferritin were done to diagnose iron deficiency anemia in both groups. Iron deficiency anemia was defined according to WHO criteria. The association of iron deficiency anemia between febrile seizure cases and controls was compared by Chi-square test. **Results:** The mean (Standard Deviation) age of cases with febrile seizures was 24.37 (15.197) months. The mean values of parameters like hemoglobin (10.4 g/dL, p=0.001), MCV (69 fL, p=0.001), MCH (26.2 pg, p=0.047), MCHC (33.08 g/dL, p=0.028) and serum ferritin (31.1ng/mL, p=0.001) among case group were significantly lower as compared to the control group. Hence iron deficiency anemia was significantly associated with febrile seizures. **Conclusion:** As iron deficiency anemia is associated with occurrence of febrile seizures, prevention and treatment of iron deficiency anemia can decrease incidence of febrile seizures.

KEYWORDS : Febrile seizures, Iron deficiency anemia, Association, Risk factor

INTRODUCTION:

Febrile seizures are the most common cause of seizures in children, occurring in 2-5% of children [1]. It is defined as the seizure that occur between the age group of 6 months to 60 months with a temperature of 38 °Celsius (100.4 °F) or higher that are not the result of central nervous system infection or any metabolic imbalance and that occur in the absence of history of prior afebrile seizures [2]. Peak age of onset is 14 to 18 months which coincides with that of iron deficiency anemia which is 6 to 24 months [3].

Febrile seizures are classified into simple (typical) and complex (atypical) types. Simple febrile seizure is a primary generalized, tonic clonic in nature lasts for few seconds to 15 minutes, occurs only once in 24 hours. Complex febrile seizures are focal, more prolonged lasting for more than 15 minutes, recurs within 24 hours. Presence of family history of epilepsy, neurodevelopmental retardation and atypical episodes increase the recurrence risk of febrile seizures and subsequent epilepsy [2]. About 39% of the emergency referrals with febrile seizures suffer from complex type. Various risk factors have been considered in the etiology of febrile seizures including familial factors, prenatal factors, present acute illness, peak temperature and anemia [4]. Febrile seizures tend to have genetic association, although the exact mode of inheritance is not known and it varies between families. Febrile seizure susceptibility trait is inherited by autosomal dominant pattern with reduced penetrance [5].

An electroencephalogram and neuroimaging studies are useful for evaluating patients presenting with complex or atypical features or with other risk factors for later epilepsy, whereas it is not usually indicated in simple febrile seizures [2].

Iron is involved in the metabolism of neurotransmitters, and enzymes monoamine and aldehyde oxidase are reduced in iron deficiency anemia. In addition, the expression of enzyme cytochrome C oxidase, a marker of neuronal metabolic activity is also decreased with iron deficiency. In developing countries, 46 to 60% of all children below the age of 4 years were found to be anemic, with half of the prevalence attributed to iron deficiency anemia. Iron deficiency is known to cause behavioral changes, poor attention span, developmental disturbances and may alter the seizure threshold of a child [6, 7]. It is considered as a risk factor for febrile seizures in children and is an easily correctable condition. Therefore, we studied the association between iron deficiency anemia and occurrence of febrile seizures.

METHODS:

This case control study was conducted at an academic, tertiary care pediatric intensive care unit (PICU), during the study period of 1st April 2020 to 31st March 2021. Ethical clearance for the study was obtained from the institutional ethical committee.

60 children between age group of 6 months and 60 months who were admitted with seizures associated with fever, were developmentally normal for age and not on any medication were included as cases. Children with CNS infection, previous history of febrile seizures, bleeding and coagulation disorder were excluded. Consecutive cases were selected for the study and 30.concurrent controls were selected from the same setting which included febrile children of age group 6 months to 60 months who presented with fever but without any seizures.

After informed written consent, the patients were evaluated with detailed history, and physical examination was done. Digital thermometer was used to check the axillary temperature of the participants at the time of admission. All findings were entered in a predesigned pretested structured proforma.

Blood samples were collected under aseptic precautions and were evaluated for complete blood count, peripheral smear examination including RBC indices (MCV, MCH, MCHC) and serum ferritin. Other investigations to exclude the various causes of seizures required for the management of case was done if necessary. The samples were processed at laboratory of Department of Pathology by trained technicians using standardized protocols. According to WHO criteria IDA will be defined as Hemoglobin <11 g/dL, MCV <70 fL, MCH <27 pg and serum ferritin <12 ng/dL [8]. Other variables that were studied includes socioeconomic status, nutrition, vaccination status, family history of seizures, type of seizure and etiology of fever.

Statistical analysis:

Data was analysed using SPSS version 21. Categorical data was represented as frequencies and percentages. Continuous data was represented as mean and standard deviation. Chi square test was used for analysis of categorical data and unpaired t-test was used for continuous data. Odds ratios were calculated for the risk factors to find the risk estimate between cases and controls. A p-value of less than 0.05 was considered as statistically significant.

RESULTS:

60 consecutive cases and 30 concurrent controls were enrolled in the study. Their demographic characteristics and hematological

parameters are depicted in Table 1 and Table 2. The mean (SD) age of cases and controls was 24.37 (15.197) and 16.73 (13.923) months respectively. Male: female ratio was 2.5:1 suggesting male preponderance of cases (71.7%). Out of 60 cases, 28 (46.7%) were from rural area and 32 (53.3%) were from urban area. Out of 30 controls 16 (53.3%) were from rural area and 14 (46.7%) were from urban area which was statistically not significant. On studying the nutritional status, 16.7% children in case group and 56.7% in control group had normal nutrition. 76.7% in case group and 40% in control group had moderate acute malnutrition. 6.7% in case group and 3.3% in control group had severe acute malnutrition, p value was 0.001 which was statistically significant. 26 (43.3%) among cases and 15 (50%) among controls were completely vaccinated, whereas, 34 (56.7%) among cases and 14 (50%) among controls were partially vaccinated, p value was 0.549 which is statistically insignificant. Maximum cases (46.7%) belonged to lower middle (III) class socioeconomic status according to Modified Kuppuswamy classification. In maximum number of children, the cause of fever in both case (63.3%) and control (53.3%) group was found to be respiratory tract infection (RTI) as depicted in figure 1.

Temperature when recorded on admission was found to be higher than normal in 40 (66.7%) out of 60 cases, in rest 20 cases it was normal, whereas only in 11 (36.7%) out of 30 controls, higher temperature was recorded at admission, in rest 19 controls it was normal (p value=0.007), which was statistically significant. The hematological parameters found to be significant after analysis were hemoglobin (Odds ratio 9.9, p value=0.001), MCV (Odds ratio 6.4, p value=0.001), MCH (Odds ratio 4, p value=0.006) and MCHC (Odds ratio 7.8, p value=0.001). Serum ferritin values (Odds ratio 3, p value=0.06) was not found to be statistically significant.

DISCUSSION:

In the present study maximum cases were between the age group of 6 to 24 months, the mean (SD) age among cases was 24.37 (15.197) and in controls it was 16.73 (13.923), and male preponderance was seen, male to female ratio been 2.5:1. Similar results were found in the study conducted by A K Saha et al [3]. In the study conducted by Rajwanti K Vaswani et al the mean age of cases was 20.78 months. Hence it is generally noted that febrile seizures was more common in second year of life [9]. In our study majority of cases presented with complex febrile seizure type (65%), study done by Ausi Indrani et al [10] also showed that patient presenting with complex febrile seizure type was more common (65%), which was contrary to study conducted by Doud et al [11] which found maximum cases with simple febrile seizure.

The mean of hematological parameters like hemoglobin, MCV, MCH, MCHC and serum ferritin were significantly lower in cases compared to controls. In our study mean serum ferritin level was significantly lower in cases (31.12±23.2 ng/mL) as compared to controls (50.54±24.6 ng/mL) (p value=0.001). Hence the present study shows that there is association of iron deficiency anemia with febrile seizure.

In the study done by Pisacane, et al [12], 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 their study. In the study done by Daoud, et al [11], the significance of iron status as a possible risk factor was evaluated. The mean serum ferritin level in the cases was 29.5mcg/L, which was much lower than the values in the controls (53.5mcg/L).

The strength of the study is that it included standardized criteria for diagnosing febrile seizures and iron deficiency anemia and there was concurrent enrollment of cases and controls. The study also had few limitations. Serum ferritin is a non specific acute phase reactant which can rise in any inflammatory condition, although in our study both cases and controls were having fever at the time of enrollment.

CONCLUSION:

Our study shows significant association of iron deficiency anemia with febrile seizures when compared to controls. Hence we can conclude that iron deficiency anemia is one of the modifiable risk factor for febrile seizure along with other risk factors such as peak temperature, family history, acute illness. All children presenting with febrile seizures should be screened for iron deficiency anemia with detail nutritional history and complete blood count. Prevention of iron deficiency anemia and possibly its treatment can decrease the incidence of febrile seizures in children of age group 6 months to 60 months.

What this study adds?

Iron deficiency anemia is a significant risk factor for febrile seizure in children of age group 6 months to 60 months.

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Conflict of interest: None

Ethical approval: The study was approved by the Institutional Ethics Committee

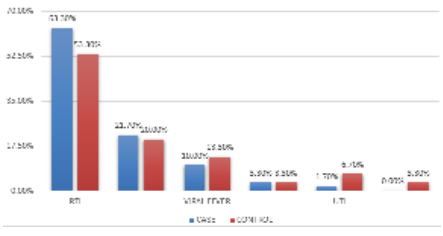
Table 1: Demographic Characteristics Of Cases And Controls In Children

Demographic characteristics	Cases (n=60)	Controls (n=30)	P value
Age(months) 6 to 24 25 to 48 49 to 60	 39(65%) 16(26.7%) 5(8.3%)	 25(83.3%) 4(13.3%) 1(3.3%)	0.193
Sex Male Female	 43(71.7%) 17(28.3%)	 17(56.7%) 13(43.3%)	0.155
Socioeconomic status Class I Class II Class III Class IV Class V	 0(0) 9(15.0) 28(46.7%) 17(28.3%) 6(10.0)	 0(0) 8(26.7) 10(33.3%) 11(36.7%) 1(3.3)	0.276
Nutrition Normal MAM SAM	 10(16.7%) 46(76.7% 4(6.7%)	 17(56.7%) 12(40%) 1(3.3%)	0.001
Temperature at admission Increased Normal	 40(66.7%) 20(33.3%)	 11(36.7%) 19(63.3%)	0.007
Family H/O seizure Present Absent	 54(90%) 6(10%)	 29(96.7%) 1(3.3%)	0.266

Table 2: Comparison Of Hematological Parameters Between Cases And Controls

Hematological Parameters	Group	N	Mean	Standard Deviation	P Value
HEMOGLOBIN (g/dL)	Case	60	10.438	1.0095	.001
	Control	30	11.617	1.0713	
MCV (fL)	Case	60	69.002	3.0773	.001
	Control	30	71.317	2.0045	
MCH (pg)	Case	60	26.200	1.7958	.047
	Control	30	26.970	1.5302	
MCHC (g/dL)	Case	60	33.085	1.6519	.028
	Control	30	33.843	1.2062	
SERUM FERRITIN (ng/mL)	Case	60	31.1208	23.28543	.001
	Control	30	50.5467	24.62590	

Figure 1: Comparison of etiology of fever between cases and controls



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