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Association of Iron Deficiency Anemia with Febrile Seizure in Children in a Tertiary Care Hospital

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ABSTRACT

Background: Febrile seizure is the most common cause of seizure in children. Iron deficiency, by lowering seizure threshold, is proposed to be one of the risk factors for febrile seizure. Many studies have been done to determine the association of iron deficiency anemia with febrile seizure but the results are controversial. Hence, the present study was conducted to evaluate the association of iron deficiency anemia with febrile seizure in Nepalese children.

Methods: A prospective age and sex matched case control study was performed in 68 cases of febrile seizures and 68 controls of febrile illness without seizure after calculating the sample size. The study was conducted from October 21, 2019 to October 20, 2020 in Pediatric ward and intensive care unit of College of Medical Sciences, Bharatpur, Nepal after obtaining ethical clearance from institutional review committee. Data entry was done in statistical packages for the social science version 20.

Results: Mean of haematological parameters (haemoglobin and mean corpuscular volume) as well as mean of serum iron, ferritin and transferrin saturation were significantly less and total iron binding capacity was significantly high in cases as compared to controls ($P < 0.05$). Iron deficiency anemia was significantly associated with cases (59.7%), with odds ratio of 2.5 (95% confidence interval =1.24 – 5.01) as compared to control (40.3%) ($P < 0.05$).

Conclusions: Iron deficiency anemia may be considered one of the risk factors for febrile seizure in children. Hence, Children with febrile seizure should be investigated and treated for Iron deficiency anemia.

Keywords: Children; febrile seizure; iron deficiency anemia

INTRODUCTION

Febrile seizure (FS), the most common childhood seizure, occurs in two to five percent of healthy children and carries 30% to 50% risk of recurrence. It usually doesn't have long term adverse outcomes, however is a frightening experience for the parents and they are concerned about the recurrence.[1, 2] Hence, it becomes important to identify the preventable risk factors so that incidence and recurrence of FS be minimised.

Iron plays an important role in myelination as well as production and release of several neurotransmitters in central nervous system. Iron deficiency anemia (IDA), by altering the level of neurotransmitters may lower seizure threshold, eventually contributing to febrile seizure.[3-7]The peak age of IDA and FS also coincide.[8]

Several studies have been conducted to establish the relationship between IDA and FS but with conflicting results.[9-15] Hence, the present study was conducted with the aim to evaluate the association of IDA with FS.

METHODS

This prospective case control study was conducted over a period of one year from October 21, 2019 to October 20, 2020 in paediatric ward and intensive care unit of College of Medical Sciences and Teaching Hospital, Bharatpur, Nepal. Ethical approval was obtained from Institutional Review Committee before commencing the study.

The sample size was determined using the proportion difference approach with the assumption of 95% confidence interval (Z = 1.96), 80% power (Z = 0.84), control to case ratio 1:1 (r =1) and based on the previous study done in Nepal where proportion of IDA in febrile seizure was 0.62 and that in controls was 0.21.[16] A total of 136 children of age group six to 60 months were recruited prospectively for the study with 68 cases and 68 controls (1:1 ratio) which was adequate for the study. An informed consent was signed by the parents or care taker of the participants after explaining them about the

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objectives and nature of study. The case group consisted of the children with normal development and who were diagnosed with febrile seizure. Controls were the age and sex matched febrile children without accompanying seizure. The children with developmental delay, electrolyte imbalance, hypoglycaemia, meningitis, encephalitis, history of taking iron supplement, history of afebrile seizure and anemia other than IDA were excluded from the study.

Febrile seizure was defined as the seizure that occurred between the age of six and 60 months with a temperature of 38 degree centigrade or higher, that was not secondary to central nervous system infection or any metabolic imbalance and in the absence of a history of prior afebrile seizure. It was further divided in two types: simple febrile seizure and complex febrile seizure. Simple febrile seizure was defined as a primary generalized, tonic clonic seizure with fever, lasting for a maximum of 15 minute, and not recurrent within 24 hour period. Complex febrile seizure was defined as more prolonged (> 15 minute), focal seizure which may recur within 24 hour.[1]

Detailed history and complete physical examination were done in all the participants and the case proforma and control proforma were duly filled. Body temperature was measured by a digital thermometer in axilla of all the participants and temperature of >38^{oC} (when 0.5^{oC} was added to it) was recorded as fever.[17]

Blood samples for complete blood count (CBC), peripheral blood smear (PBS), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), serum iron (Fe), total iron binding capacity (TIBC), transferrin saturation (TS) were investigated for all participants. Plasma ferritin (PF) was estimated once when they were afebrile. The complete blood count was analysed by an automatic compact six differential haematology analyzer, Yumizen H 550. Serum Fe, TIBC and TS were estimated by fully automated BioSystem BA400 LED based on spectrophotometric technique. Plasma ferritin was estimated by MAGLUMI 2000 plus Chemiluminescence Immunoassay (CLIA) system. Urine routine examination, urine culture, blood culture, cerebrospinal fluid culture and chest x-ray were done when required. All the tests were done by a laboratory personnel who was unknown to the purpose of the study. The diagnosis of IDA was made by a pediatrician without knowing the groups to which each of the test results belonged. The normal level of serum iron (Fe) was determined as Fe >40 µg/dl for children younger than one year of age and Fe >50 µg/dl for children over one year of age. The normal range of TIBC was considered 210-430 µg/dl. Iron deficiency anemia was defined as haemoglobin (Hb) level <11 gm/dl, TS <16%, PF <30 µg/l, and MCV <70 fl.[14, 18-20]

The data was entered and analysed in Statistical Package for Social Sciences (SPSS) 20.0. In the descriptive statistics, frequency, percentage, mean and standard deviation (SD) were calculated while in the inferential statistics, chi-square was used for qualitative variables and unpaired T- test for quantitative variables. P-value <0.05 was considered statistically significant. Odds ratio was calculated by logistic regression at confidence interval (CI) of 95%.

RESULTS

There was no significant difference in age and sex as well as peak mean temperature between case group and control group. Stunting had statistically significant association with febrile seizure (Table 1).

Table 1. Comparison of baseline characterisitics between cases and controls.

Variable	Case (%)	Control (%)	P-value
Mean age (months)	23.90±14.53	25.80±14.97	0.46
Sex			
Male	40 (58.8)	40 (58.8)	0.56
Female	28 (41.2)	28 (41.2)	
Peak mean temperature (°C)	39.63±0.83	39.30±1.46	0.11
Underweight	9 (13.2)	5 (7.4)	0.19
Stunting	13 (19.1)	5 (7.4)	0.03
Wasting	9 (13.2)	3 (4.4)	0.06
Exclusive breastfeeding	43 (63.2)	48 (70.6)	0.36
Family history of febrile seizure	2 (2.9)	0 (0.0)	

The most common etiology of fever in FS was upper respiratory tract infecton 45 (66.2%) whereas, that in control was Lower respiratory tract infection 24 (35.3%) (Table 2).

Table 2. Etiology of fever in cases and controls.

Etiology	Case (%)	Control (%)
Upper respiratory tract infections	45 (66.2)	23 (33.8)
Acute gastroenteritis	5 (7.4)	10 (14.7)
Lower respiratory tract infectons	5 (7.4)	24 (35.3)
Acute otitis media	2 (2.9)	4 (5.9)

Urinary tract infection	3 (4.4)	5 (7.4)
Pyoderma	0 (0.0)	1 (1.5)
Dengue	0 (0.0)	1 (1.5)
Fever without localising sign	9 (13.2)	1 (1.5)

Hematological parameters such as Hb, MCV, serum Fe, TS and PF were significantly low and TIBC was significantly high in febrile seizure in comparison to controls (P-value <0.05) (Table3).

Table 3. Comparison of hematological and Iron profile between cases and controls.

Variables	Group	Mean	Standard deviation	P-value
Hb	Case	10.36	1.70	0.01
	Control	11.19	1.95	
MCV	Case	67.95	8.41	0.01
	Control	71.65	9.66	
MCH	Case	23.67	3.26	0.26
	Control	24.43	4.49	
MCHC	Case	31.94	2.21	0.45
	Control	32.23	2.41	
Iron	Case	24.02	16.78	0.00
	Control	43.38	22.05	
TIBC	Case	372.09	87.90	0.03
	Control	321.69	104.24	
Transferrin saturation	Case	7.42	9.15	0.00
	Control	15.35	10.31	
Ferritin	Case	30.07	27.32	0.04
	Control	40.92	35.09	

Iron deficiency anemia had statistically significant association with cases as compared to control (P-value <0.05) with OR of 2.5 (95% CI = 1.24 - 5.01). However, there was no significant difference in the association of IDA between either types of febrile seizure (Table 4 and 5).

Table 4. Frequency distribution of IDA in cases versus controls.

Group	Case	Control	Odds ratio	95% CI	P-value
IDA present (n/%)	46 (59.7)	31 (40.3)	2.50	1.24 - 5.01	0.01
IDA absent (n/%)	22 (37.3)	37 (62.7)			
Total	68 (100)	68 (100)			

Table 5. Frequency distribution of IDA in simple febrile seizure and complex febrile seizure.

Type	Simple febrile seizure	Complex febrile seizure	P value
IDA present (n/%)	35 (68.6)	11 (64.7)	0.77
IDA absent (n/%)	16 (31.4)	6 (35.3)	
Total	51 (100)	17 (100)	

DISCUSSION

In our study, the mean of hematological indices like Hb and MCV were significantly less in cases than the controls. These findings are similar to previous studies done in Pakistan, Jordan and Nepal.[12,16,21] The mean of serum iron, PF and TS were also significantly lower and TIBC was significantly higher in cases than the controls as observed in other studies.[11,12,16,21] The present study showed significant association of IDA with the cases (59.7%) as compared to controls (40.3%). Iron plays a crucial role in transport of oxygen to brain. Levels of neurotransmitters in brain such as nor-adrenaline, dopamine, glutamate, Gamma amino butyric acid (GABA) and serotonin are altered during its deficiency which explains some of the cognitive, behavioural, motor and developmental changes that occur in children especially during the first two years of life. Furthermore, iron deficiency (ID) is associated with several neurological disorders such as restless leg syndrome, breath-holding spells, and attention deficit hyperactive disorders. It causes lowering of seizure threshold by stimulating the function of neurons and decreasing the metabolism of neurotransmitter, eventually resulting in convulsions.[3-6] Recently, Rudy et al. demonstrated that the mice which were postnatally exposed to ID had a decreased seizure threshold and increased susceptibility to certain types of seizure.[7] Moreover, fever can worsen the effect of anemia or ID in brain and therefore, can cause convulsion.[10,11]

Febrile seizure recurs in approximately 30% of children experiencing a first episode, in 50% after two or more episodes and in 50% of children younger than one year at febrile seizure onset. There are many risk factors for recurrence of febrile seizure such as younger age at onset, duration of fever < 24 hour, low grade fever (38^{0C} to 39^{0C}), family history of febrile seizures or epilepsy and maternal smoking and alcohol consumption during pregnancy.[1,10,22] Iron deficiency as a risk factor for febrile seizure has also been studied extensively but with conflicting results. In study done by Pisacane et al., IDA was significantly higher in their case group (30%) as compared to the conrol group (14%).[10] Similar results were obtained in a study done by Ghasemi et al. where 40% of cases had IDA when compared to 26%

of controls.[11] A study done in Pakistan also showed the significant association of IDA with febrile seizure than with controls.[12] Another study done in India also demontrated that 68% of cases were iron deficient compared to 30% of controls.[23] A recent meta-analysis of 17 case-control studies concluded that IDA is associated with an increased risk of FS.[13] Another metaanalysis which studied 21 articles also reported that IDA was more prevalent among FS patients when compared with the controls and the overall OR was 1.53 (95% CI = 1.46 to 2.85).[3] In contrast, a case control study of 25 cases and 26 controls done by Kobrinsky et al described that IDA increased the threshold of febrile seizure and that lack of iron might protect against the development of FS.[24] In a similar study by Derakhshanfar et al., incidence of IDA was significatly higher in controls compared with cases concluding that the risk of FS in anemic children is less common as compared to non anemic ones. They also added that iron defciency may alter the level of excitatory neurotransmitters like monoamine oxidase and aldehyde oxidase leading to decreased excitation of the neurons. [20] Likewise, in a study done in Iran, the prevalence of anemia in the case group (22.5%) was significantly less than that in the control group (34%).[9] There are also studies showing no significant association of IDA with FS. For example, in a study by Amirsalari et al., low plasma ferritin was found in 26.5% of cases compared to 29.5% of controls and low hemoglobin was found in 3% of cases compared to 6.8% of controls, but there was no significant difference between the two groups, demonstrating no relationship between IDA and FS.[14] In another study by Bidabadi et al., IDA was less frequent among cases as compared to controls and they suggested that there is no protective effect of iron deficiency against febrile seizure.[15] These inconsistent results of different studies in determining the relationship between ID/IDA and FS may be due to differences in socioeconomic status, nutritional status, ethnic backgrounds, age groups, causes of fever, sample sizes, as well as criteria to define anemia and iron deficiency.

Iron is an essential micronutrient that affects the immunity, health and nutritional status of children. Its deficiency may cause poor health and recurrent infections, which may lower the seizure threshold resulting in seizure, especially in children in developing countries.[25, 26] In our study also, underweight, stunting and wasting were associated more with febrile seizure than with cotnrols. However, only stunting had significant association with the cases in comparison with controls. Another Nepalese study also showed that more cases (58.4%) were underweight than the controls (41.6%) but was not statistically significant.[16] A study done in Iran also didn't show signficant association of failure to thrive with febrile seizure.[17]

The present study didn't show significant difference in assocation of IDA between the two types of FS: simple and complex febrile seizure. This finding is in accordance with a recent study done in South Korea where none of the hematological parameters showed any significant difference between simple and complex febrile seizure.[27] Another study done in Jordan demonstrated significantly low Hb level in complex febrile seizure as compared to simple febrile seizure, however, there was no significant difference in PF between the two types.[21]

In our study, the odds ratio of IDA for the FS group was 2.5 times that of the control group. This finding accords to the study done by Pisacane et al and Ghasemi et al where OR of IDA for FS was nearly two times than that of controls.[10, 11] Previous study done in Nepal also showed odds ratio of IDA for FS nearly six times that of controls.[16]

It is hospital based with small sample size and plasma ferritin, being an acute phase reactant may be the confounding factor. However, both the groups were recruited during febrile state and blood samples for PF were drawn and investigated during afebrile period. The strength of this study are its prospective design, multiple indices taken to define IDA and the location in southern central Nepal in contrast to many other studies.

CONCLUSIONS

Iron deficiency anemia was significantly associated with febrile seizure. Hence iron deficiency may be considered one of the risk factors for FS in children. Children with FS should be investigated and treated for IDA. Iron supplements should be prescribed for the children in developing countries where there is high prevalence of IDA as well as in children with other known risk factors for FS. Further studies are required to determine the underlying pathophysiology of how iron deficiency lowers the seizure threshold. Also, further prospective studies on large population are required to evaluate the association of IDA with FS as well as if iron supplementation can prevent the occurrence of FS.

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