Clinico-Demographic Profile of Febrile Seizure and Its Association With Iron Deficiency

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ABSTRACT

Introduction: Febrile seizure (FS) is recognised as the most frequent type of seizure in children (age six months to five years). This observational study was conducted in our hospital to assess any possible association of febrile convulsion with iron deficiency anaemia (IDA) and to see the incidence of iron deficiency in six months to five years old children.

Methods: Eighty eight Simple febrile seizure patients of age six months to five years fulfilled the inclusion criteria and were enrolled between April 2018–March 2019. A pre-designed proforma including detailed history, physical examinations, systemic examinations and relevant investigations were filled-up.

Results: Eighty eight subjects with FS were studied. Occurrence of IDA was 67.04% among them. Age was significantly associated with haemoglobin (Hb%) (p-value = 0.000), severity of anaemia (p-value = 0.000), mean corpuscular volume (MCV) (p-value = 0.000), mean corpuscular haemoglobin (MCH) (p-value = 0.000), mean corpuscular haemoglobin concentration (MCHC) (p-value = 0.000) and serum ferritin (p-value = 0.000). However, no significant association between Hb% and gender was found (p-value = 0.890).

Conclusions: Considering the clinico-demographic context of the present study and extent of anxiety and worries of parents of FS children, it is imperative to initiate FS prevention and control programme. Nearly two-third of study subjects had significant low serum ferritin indicating association of simple febrile seizure with IDA. However, prevalence of IDA as a risk factor for FS needs to be studied on adequate and representative sample so that iron supplementation could be started as an inbuilt strategy of simple febrile seizure management.

Key words: ferritin; haemoglobin; MCH; MCHC; MCV

INTRODUCTION

Febrile seizure (FS) is recognised as the most common neurologic disorder and the most frequent type of seizure in children. It is defined as "a seizure occurring in febrile children between the ages of six to 60 months who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizure" by American Academy of Paediatrics (AAP) (2008).[1] Although, it has good outcomes without any clinical consequences, it still has a strong possibility of epilepsy in future[2], as well as rate of recurrence is 30% and 50% after the first and the second occurrences respectively[3] so, there is need to identify correctable risk factors to reduce the prevalence of FS and hence, of epilepsy and convulsion.[4,5]

The overlapping of age for peak incidence of FS (i.e. from 14 to 18 months of age) with that of iron deficiency anaemia (i.e. from six to 24 months of age) suggests possible association between them.[6] Iron is an important micronutrient for almost all the cells in human body and acts as a co-factor for several enzymes necessary for neurochemical reactions[7,8], myelin formation[9] and brain energy metabolism.[10] Thus its deficiency leads to defective myelination, metabolism of mono-amine oxidase and aldehyde oxidase, as well as synthesis of tyrosine and tryptophan hydroxylase which are essential for synthesis and release of neurotransmitters like serotonin, dopamine and gamma-amino butyric acid (GABA)[11,12] which in turn are responsible for change in the amplitude and the threshold of neurons excitation.[13]

Therefore, we determined to study the relationship between prevalence of iron deficiency anaemia (IDA) and incidence of FS among children of age ranging from six months to five years in India. The incidence of FS in India is similar to western figures.[14,15] The National Family Health Survey-3 (NFHS-3) data states that around 80 per cent children under three years of age have anaemia in India. Hence, we conducted the present observational study in our centre and tried to increase the strength of evidence regarding iron deficiency as a risk factor for febrile seizure because it is evident that iron deficiency anaemia is correctable and remediable condition[16] and thus, incidence of FS could be decreased by treating nutritional anaemia with diet and iron supplements.

METHODS

Six months to five years old children with FS brought to our centre and treated in paediatric OPD or admitted in indoor paediatric department depending upon the general condition, were candidates for the study. Emergency treatment was given to stabilise the patient. This observational study was approved by institutional ethical committee and the consent was obtained from parents of each patient who fulfilled the criteria of simple FS before enrolment in the study. Detailed history (demographic data, seizure details, nature of febrile illness including the duration of fever within 24 hours of seizure and other details such as family history of febrile seizures/epilepsy and history of neurodevelopmental problems, temperature at admission, and nutritional status) were recorded. Physical examination including a thorough neurological examination was done. Venous blood sample was collected and sent to the pathology department for investigations. IDA was diagnosed on the basis of the following investigations – Haemoglobin (Hb%), peripheral blood smear, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width (RDW), serum ferritin and total iron binding capacity (TIBC). Hb%, MCH, MCV, MCHC, RDW and TIBC were measured using automated analyser whereas ferritin by electrochemiluminescence immunoassay method and peripheral blood smear was examined under microscope to look for microcytosis and hypochromia. Equipment used were: analog mercury thermometer (Hicks) for temperature (in degree Fahrenheit), non-stretchable measuring tape (cross tape method) for head circumference, weighing machine based on spring balance (pan type for infants and platform type for children greater than one year age) for weight, infantometer for length and stadiometer for height measurement along with sysmex XP-100 haematology analyser for complete haemogram and ERBA EM-200 for TIBC analysis.

We considered iron deficiency anaemia in a child if Hb% < 11 g/dL; MCV, MCH and MCHC < - 2 SD and ferritin < 30 ng/dL as per age (according to WHO) for six months to four years 11 months and similarly, Hb% < 11.5 g/dL, MCV, MCH, MCHC < - 2 SD and ferritin < 15 ng/dL as per age (according to WHO) for ≥ four years 11 months old child. MCHC, MCH, MCV, and peripheral blood smear were used to rule out other causes of anaemia. In the present study, normal ferritin level was considered when it was > 30 ng/dL for healthy children and reduced if < 30 ng/dL for children with infection.

All relevant data of 88 patients with FS were compiled using Microsoft Excel sheet version 2016 and analysed using SPSS version 22.0 (SPSS Inc. Chicago, Illinois, USA). Frequency (%) for different variables were calculated. Categorical variables were analysed using Chi-square test as applicable for statistical association and inference. Correlation was considered statistically significant with p-value < 0.05.

RESULTS

Our results mainly showing general characteristics of study subjects (N = 88) (Table 1), with their distribution according to severity of anaemia (Table 2), MCV, MCH and MCHC values (Table 3) and ferritin level (Table 4) in different age groups.

Here, we found that the incidence of FS decreased with increasing age where majority of children (68.2 %) belonged to the age group six months to one year 11 months followed by the age group > one year 11 months to four years 11 months (29.5%) (Table 1). Mean age of involved children was 20.58 months with standard deviation of 14.03 months.

The percentage of female patients involved was less (46.59%) than that of male patients (53.40%) (Table 1). Male to female ratio was 1.14:1. Most of children were suffering from moderate anaemia (56.81%), mild anaemia was found in 17.04% of enrolled children and none of them had severe anaemia (Table 2).

The values of MCV, MCH and MCHC < - 2 SD were found in 59 (67.04%), 68 (77.27%) and 65 (73.86%) patients respectively and majority of study subjects belonging to age six months to one year 11 months had low values of red cell indices {value of MCV, MCH and MCHC < - 2 SD were 46 (52.3%), 51 (58.0%) and 48 (54.5%) respectively} (Table 3). Nearly two-third (67.04%) patients had low ferritin level including 58 patients of age < five years (Table 4).

Table 1. General characteristics of study subjects

Variables		No	%
Age	6 m - 1 yr 11 m	60	68.2
	> 1 yr 11m - 4 yr 11 m	26	29.5
	> 4 yr 11 m	2	2.3
Sex	Female	41	46.59
	Male	47	53.40
Temperature within 24 hr of seizure	> 99 - 100°F	0	0
	>100 - 101°F	63	71.59
	>101 - 102°F	25	28.40
Duration of seizure (in min)	< 5	25	28.40
	≥ 5	63	71.59
Total no. of seizure (in life) at presentation	1st Episode	72	81.8
	2nd Episode	13	14.8
	> 2nd Episode	3	3.4
Family history	No	39	44.31
	Yes	49	55.68
Anaemia	Absent	23	26.13
	Present	65	73.86

Age was significantly associated with Hb% (p-value = 0.000), severity of anaemia (p-value = 0.000) (Table 2), MCV (p-value = 0.000), MCH (p-value = 0.000), MCHC (p-value = 0.000) (Table 3) and serum ferritin (p-value = 0.000) (Table 4). But no significant association was found between Hb% and gender (p-value = 0.890).

DISCUSSION

Several risk factors for FS in children have been described in literatures and one of those risk factors is iron deficiency.[5,17,18] In past several decades, many studies have been conducted to establish a

Table 2. Distribution of study subjects based on severity of anaemia in different age

Age	Anaemia				Total
6 months to 4 yr 11 months	**No anaemia (Hb% ≥ 11g/dL)**	**Mild anaemia (Hb%10 - 10.9 g/dL)**	**Moderate anaemia (Hb% 7 - 9.9 g/dL)**	**Severe anaemia (Hb% < 7 g/dL)**	
Frequency	23	13	50	0	86
Percentage	26.74	15.11	58.13	0	100
> 4 yr 11 months to 5 years	**No anaemia (Hb% ≥ 11.5g/dL)**	**Mild anaemia (Hb% 11 - 11.4 g/dL)**	**Moderate anaemia (Hb%8 - 10.9 g/dL)**	**Severe anaemia (Hb% < 8 g/dL)**	
Frequency	0	2	0	0	2
Percentage	0	100	0	0	100

definite correlation between them and to stamp IDA as a risk factor for FS among under five years old children. Here, in the present study, we considered the hypothesis of positive relationship between FS and IDA. So, we worked in line of this hypothesis to make a conclusion whether really IDA would be a risk factor for FS or would disapprove our notion. In order to find out any possible association between FS and IDA, this observational study was undertaken in our tertiary care hospital after enrolling 88 patients and it has been found that IDA increases incidence of FS in six months to five years old children.

Majority of the study subjects had experienced the first FS in one year to one year 11 months age in our study. We found that with advancing age, prevalence of FS was decreasing after four years 11 months age, supported by Hesdorffer and Sugai where authors also reported lower incidence before six months or after three years age and concluded that the incidence of FS decreases markedly after four years of age and rarely occurs in children older than seven years of age[19,20] and the peak incidence at around 18 months of age. Thus, age plays an important role in the susceptibility of FS, but the risk of recurrence of seizure declines with age of

Table 3. Distribution of study subjects based on MCV, MCH and MCHC values in different age group

Age	6 months to 1 yr 11 months		yr to 4 yr 11 months		5 yr		Total
MCV (f/L)	**< 67 (< - 2SD)**	**≥67 (≥ - 2SD)**	**< 73 (< - 2SD)**	**≥73 (≥ - 2SD)**	**< 74 (< - 2SD)**	**≥74(≥ - 2SD)**	
Frequency	46	14	12	14	1	1	88
Percentage	52.3	15.9	13.64	15.9	1.14	1.14	100
	X^2=1.760E2; df=10;P=0.000						
MCH (pg)	**< 22 (< - 2SD)**	**≥22 (≥ - 2SD)**	**< 25 (< - 2SD)**	**≥ 25 (≥ - 2SD)**	**< 25 (< - 2SD)**	**≥ 25 (≥ - 2SD)**	
Frequency	51	9	16	10	1	1	88
Percentage	58.0	10.2	18.2	11.4	1.14	1.14	100
	X^2=88.326; df=6;P=0.000						
MCHC (g/L)	**< 32 (< - 2SD)**	**≥32 (≥ - 2SD)**	**< 32 (< - 2SD)**	**≥32 (≥ - 2SD)**	**<32 (< - 2SD)**	**≥32 (≥ - 2SD)**	
Frequency	48	12	16	9	1	1	88
Percentage	54.5	13.6	18.2	10.2	1.14	1.14	100
	X^2=1.712E2; df=10;P=0.000						

Table 4. Distribution of study subjects based on ferritin level in different age group

Age	Ferritin (ng/dL)	No.	Percentage	Test of significance
< 5 yr	< 30	58	65.9	
	≥ 30	28	31.8	
≥ 5 yr	< 15	1	1.14	$X^2 = 88.000$ df = 3
	≥ 15	1	1.14	p = 0.000
Total		88	100	

growing child.[21] Literature shows that approximately 6–15% of children can have FS after four years, and onset after six years is unusual. Regardless of the population, most of the data support the unique age specificity of the maturing brain's sensitivity to fever. Although the mechanism of this increased susceptibility is unclear, animal models suggest that there is enhanced neuronal excitability during the normal brain maturation.[22] So, this may be a cause that lead to FS in a specific age group.

IDA is one of the most common nutrition related problems in the world. In developing countries 46-66% of under five years old children are anaemic. In India as per The National Family Health Survey-3 (NFHS-3), 70% of under five years old children are anaemic. In the present study, we tried to determine the iron status with the help of Hb%, MCV, MCH, MCHC and ferritin level as overlapping of age for peak incidence of FS (i.e. from 14 to 18 months of age) with that of IDA (i.e. from six to 24 months of age) indicates association between them.[8] We found that 73.86% of study subjects were anaemic while that of 26.13% were non-anaemic according to Hb% level as per WHO guideline. The value of MCV, MCH and MCHC < -2 SD were found in 67.04%, 77.27% and 73.86% study subjects respectively and serum ferritin was also low. Age was significantly associated with Hb % (p-value = 0.000), severity of anaemia (p-value = 0.000), MCV (p-value = 0.000), MCH (p-value = 0.000), MCHC (p-value = 0.000) and serum ferritin (p-value = 0.000). No significant association between Hb% and gender was found (p-value = 0.890). Statistically, the results of present study were consistent with findings of the study conducted by Piscane[17] and Kumari PL.[18] In contrary, Kobrinsky[23] in Fargo, reported higher Hb% and MCV values among patients with FS. Bidabadi E et al.[24], Daoud AS et al.[4] and Vaswani RK et al.[25] also found higher Hb%, MCV, MCH, and MCHC among cases than controls and were unable to establish any significant difference between the two groups statistically.

We found that two-third of the study subjects had lower ferritin level. This result showed similarity with studies done by Daoud AS et al.[4], Piscane A et al.[17], Moeman A et al.[26] and Fallah R et al.[27] where the mean plasma ferritin level in the FS group was lower than the control group and they found serum ferritin to be statistically correlating with FS.

However, there are few limitations of the present study including inability to rule out some confounding factors causing IDA like lead poisoning, short period of study, and as study was conducted in a single tertiary health care centre, it does not represent the whole population.

CONCLUSIONS

On the basis of results of the present study, following conclusions were drawn: FS has slight male predominance over female, most of the subjects (71.59%) had fever >100 - 101°F within 24 hours of seizure, short duration (not >15 minutes) of seizure, as high as three-fourth (71.59%) subjects had seizure for ≥ five minutes but not more than 15 minutes duration, subjects with the first episode of FS were found in majority of cases, positive family history was also present in more than half of the study subjects, prevalence of FS was decreasing with advancing age and rising body temperature before or after febrile seizure was not significantly affected by age and gender. Nearly three-fourth of study population were found anaemic and it was significantly correlated with age but not with gender. Prevalence of moderate type of anaemia was observed in around two-third subjects belonged to age group six months to one year 11 months. Significant association between age of study subjects and red cell indices as well as low ferritin in anaemic children with FS were noticed. However, no significant association between Hb%

and gender of different age groups in children with FS was found. So, considering the clinico-demographic context of the present study and extent of anxiety and worries of parents of FS children, it is imperative to initiate FS prevention and control programme. But, prevalence of IDA as a risk factor for FS needs to be studied on adequate and representative sample and therefore, there is need for undertaking effective trial with long term follow-up to demonstrate effectiveness of iron supplementation in FS in community involving larger population, so that iron supplementation could be started as an inbuilt strategy of FS management.

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