The association of iron deficiency anaemia with simple febrile seizures in children less than 5 years age: A single centre, prospective, case-control study

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Abstract
Introduction: Febrile seizure (FS) has an incidence of 2-5% in the neurologically healthy child. Among various risk factors, iron deficiency anaemia (IDA) is implicated in the increased risk of FS.

Objectives: To primarily assess the association between IDA and simple FS and secondarily the association of other risk factors with simple FS.

Method: This was a single centre, prospective, case control study involving 120 children, aged between 6 months and 5 years, 60 presenting with simple FS (cases) and 60 presenting with acute febrile episodes without seizures (controls). The study was performed from September 2017 to August 2019. Cases and controls were matched for age, sex, weight, and height. Laboratory investigations such as complete blood count, serum iron (SI), total iron binding capacity (TIBC), and SI/TIBC index were performed and compared between the two groups.

Results: Compared to controls, significantly higher number of cases had a family history of FS and family history of seizure disorder (both p-values<0.05). Moreover, as compared to controls, cases had significantly lower median haemoglobin levels, mean corpuscular volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration (all p-values<0.05). However, cases had significantly higher median red cell distribution width (p-value = 0.004). Similarly, cases had a significantly lower mean SI levels, and SI/TIBC index, as compared to controls (both p-values<0.05). However, cases had significantly higher mean TIBC (p-values<0.05). Finally, as compared to the controls, cases with IDA had 8.4 fold increased risk of developing the FS.

Conclusions: The findings of this study suggest that IDA is a risk factor for the development of FS in children aged <5 years.

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(Key words: Anaemia, children, febrile seizures, iron deficiency, serum iron, total iron binding capacity)

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Introduction

Febrile seizure (FS) has an incidence of 2-5% in the neurologically healthy child[1-3]. It is particularly prevalent amongst the Asian population and has a predilection for male sex[4]. The exact aetiology of FS remains unknown. Some studies have demonstrated a strong family history of FS in siblings and parents, suggesting a genetic predisposition, while other studies have implicated environmental factors in its causation[5]. Thus, multiple risk factors have been suggested to result in FS[4]. Amongst children, the maximum incidence of iron deficiency anemia (IDA) is reported to be in the 6 months to 2 year age group and this coincides with the FS peak incidence age group[6]. However, research studies have conflicting reports explaining the link between FS and IDA amongst children[7-9]. In these studies, a few authors have concluded that iron deprivation plays a role in the pathogenesis of FS, while others disproved the causative role of IDA in FS. Studies have reported a higher prevalence of IDA and FS in Central India[8]. However, the association between them has not been studied.

Objectives

To primarily assess the association between IDA and simple FS and secondarily the association of other risk factors such as family history of FS and family history of seizure disorders with simple FS.

Method

A prospective, single centre, case-control study, involving 120 subjects (60 cases and 60 controls) visiting the Out-patient Department (OPD) and admitted in the wards of Paediatric Department, Indira Gandhi Government Medical College and

Hospital, Nagpur, was conducted from September 2017 to August 2019.

Eligibility criteria

Cases of either sex, 6 months to 5 years old, presenting with simple FS, were included in the study. Similarly, controls were enrolled except that they presented with acute febrile illness (AFI) without seizures (AFI >24 hours, up to 48 hours without any CNS involvement). However, cases and controls with neurological infections, delayed development, those already on iron therapy, and previously diagnosed anaemia of other causes were excluded. Additionally, controls with past history of febrile seizures and seizure disorders were excluded. Screening investigations were carried out and the eligible candidates were included in the study.

Procedure

After admission, information related to age, gender, height, weight, and family history of FS and family history of seizure disorder were obtained from both cases and controls, while, information related to the family history of seizure disorder was noted only in the cases. The data were then entered into a predesigned structured case record form. All the subjects received an appropriate diet (including iron-rich food such as groundnuts, jaggery, green-leafy vegetables, and non-vegetarian diet) for their ages and were free of any feeding-related problems such as limited appetite; resistance to feeding; partial or total refusal of foods according to its texture, colour, smell, consistency, or taste; and organic causes including food allergy, coeliac disease, oesophagitis, gastro-oesophageal reflux, and others. Both cases and controls were matched for age, sex, height, and weight.

The cases were diagnosed as having simple FS, if the seizure was primary generalized, usually tonic-clonic, associated with fever (≥ 38 ºC), remained for not more than 15 minutes, and did not recur within a period of 24 hours[10]. The general examination included the measurement of height and weight of the subjects. For children 2 years and below, infantometer was used and stadiometer was used for the children aged > 2 years. The portable digital weighing machines (different machines for children 2 years and below and >2 years) were used to weigh the children.

Laboratory investigations

Investigations on admission included complete blood count (CBC), serum iron (SI), total iron binding capacity (TIBC), and SI: TIBC ratio. Clinical evaluation was performed to rule out other causes of anaemia.

In 6 month to 5 year old children, the normal level of SI and SI: TIBC ratio were 60-170 µg/dl (10-30µmol/L) and 20 - 50%, respectively. The normal range of TIBC in infants was 100-400 µg/dl, and thereafter, 250-400 µg/dl[10,11]. All blood counts were calculated by Sysmex XS-800i CBC machine (Norderstedt Germany) and serum iron and TIBC were calculated by Biochemical Systems International SpA – 3000 Evolution (Arezzo (AR) - Italia).

Anaemia was defined as a Hb level <11g/dL. Iron deficiency was defined as SI <40 µg/dL (for subjects <1 year of age) and <50 µg/dL (for subjects 2–5 year of age), or transferrin saturation <16%.[12]

Sample size calculation

Anticipated probabilities of IDA in cases (P1) was 0.22 and odds ratio (OR) was 3.16.[13]

The P2 was calculated by the formula:

$$P2 = \frac{P1}{OR\,(1-P1) + P1}$$

Value of normal deviation at 5% confidence interval (Z1-α) and 80% power of the study (Z1-β) were considered to be 1.64 and 0.842, respectively.

Thus, the final sample size was calculated based on the formula:

$$N = \frac{[Z1-\alpha\sqrt{2P2(1-P2)} + Z1-\beta\sqrt{P1(1-P1)+P2(1-P2)}]^2}{(P1-P2)^2}$$

= 60. Thus, the sample was found to be 120, with 60 subjects in cases group and 60 subjects in control group.

Ethical issues: Ethical clearance was obtained from the Ethics Committee of Indira Gandhi Government Medical College and Hospital, Nagpur, India. After explaining the study procedures, an assent from the subjects and written informed consent from the parents was obtained

Statistical analysis

Qualitative variables are expressed as frequencies (%) and continuous variables as mean (± SD) or median (interquartile range). Various haematological parameters were compared between cases and controls. After checking normality of the data by Shapiro-Wilk test, we performed Mann-Whitney U tests for non-normally distributed data and independent t-tests for normally distributed data. A Chi-square test was performed to compare qualitative variables, between case and control. A two-tailed probability (p) value of less than 0.05 was considered as statistically significant. Data analysis was performed with the help of Statistical Package for Social Sciences Software, version 23.0 (SPSS, IBM Inc, Chicago, Illinois, USA).

Results

Majority of children in both groups were males i.e. cases (58.3%) and controls (65%). Most of the subjects in both groups belonged to 0.5 to 2 years of age i.e., cases (63.3%) and controls (66.7%). Moreover, there was no significant difference between subjects in terms of distribution in various age groups i.e., 0.5–2 years (p = 0.702), 2.1–4 years (p = 0.841), and 4.1–5 years (p = 0.697). Finally, there was no significant difference between subjects in both groups in terms of sex (p = 0.453), median age (p = 0.675), weight (p = 0.104), and height (p = 0.912). Thus, the cases and controls were matched in terms of sex, age, weight, and height (Table 1).

Table 1: ***Matching of cases and controls (according to gender, age, weight, and height)***

	Cases	Controls	p-value
Male n (%)	35 (58.33)	39 (65)	0.453#
Female n (%)	25 (41.67)	21 (35)	
Age in years Median (IQR)	2 (1 – 4)	2 (1 – 3)	0.675*
Weight in kg Median (IQR)	10 (8.35 – 12.00)	8.5 (7.8 – 11.88)	0.104*
Height in cm Median (IQR)	82 (72.50 – 89.50)	83 (73.00 – 92.75)	0.912*

*Non-parametric variables presented as frequency (percentages); Skewed variables presented as median (interquartile range); # Chi-square test; *Mann-Whitney U test; p-value <0.05 was considered as statistically significant*

It was observed that pallor (p<0.0001), pica (p<0.0001), and platynychia (p<0.0001) were more prevalent amongst cases than controls. Moreover, as compared to controls, cases had significantly higher number of subjects with family history of FS (p<0.0001). Similarly, cases had significantly higher number of subjects with family history of seizure disorder, as compared to controls (p = 0.012) (Table 2).

Table 2: ***Distribution of study groups according to clinical features, family history & past history of seizures***

Clinical features	Cases (*n = 60*) n (%)	Controls (*n = 60*) n (%)	p-value
Pallor	38 (63.3)	16 (26.7)	< 0.0001*
Pica	43 (71.7)	21 (35.0)	< 0.0001*
Platynychia	15 (25.0)	01 (01.7)	< 0.0001*
Family history of febrile seizures			
Yes	13 (21.7)	0 (0)	< 0.0001
No	47 (78.3)	60 (100)	
Family history of seizure disorder			
Yes	13 (21.7)	0 (0)	0.012
No	47 (78.3)	60 (100)	

*Non-parametric variables presented as frequency (percentages); *Chi-square test; p-value <0.05 was considered as statistically significant*

On CBC analysis, there were significantly higher number of cases with anaemia i.e. Hb <11 g%, as compared to controls (35 *vs* 13; p <0.0001). Moreover, as compared to controls, significantly higher number of cases had Hb levels in the range of 6-8 g% (p = 0.013) and 8-11 g% (p = 0.007). On further analysis, it was observed that median Hb levels (p <0.0001), median MCV (p = 0.006), median MCH (p <0.0001), and median MCHC (p <0.0001) were significantly lower amongst cases than controls. However, as compared to controls, cases had significantly higher median RDW (p = 0.004) (Table 3).

Table 3: ***Comparison of cases and controls according to severity of anaemia and haematological parameters***

Severity of anaemia (Hb)	Cases (*n = 35)*	Controls (*n = 13)*	p-value
< 6 g %	1	1	1.000*
6 – 8 g %	12	3	0.013*
8 – 11 g %	22	9	0.007*
CBC parameters			
Hb (g %) Median (IQR)	10.05 (8.43 – 11.98)	12.10 (11.53 – 12.80)	< 0.0001*
MCV (fl) Median (IQR)	69.25 (62.90 – 77.25)	74.35 (72.55 – 77.33)	0.006*
MCH (pg/cell) Median (IQR)	22.10 (19.30 – 25.40)	26.18 (24.10 – 28.08)	< 0.0001*
MCHC (g/dl) Median (IQR)	30.75 (26.33 – 33.10)	34.80 (32.13 – 36.95)	< 0.0001*
RDW (%) Median (IQR)	18.00 (12.63 – 21.88)	13.10 (12.33 – 15.08)	0.004*

*Non-parametric variables presented as frequency (percentages); *Chi-square test; p-value <0.05 was considered as statistically significant.*

On evaluating the SI and TIBC, cases were found to have a significantly lower mean SI levels (p = 0.044), and lower median SI/TIBC index (p = 0.004) than controls. However, as compared to controls, cases had significantly higher mean TIBC (p = 0.006) (Table 4).

Moreover, significantly higher number of cases had SI and SI/TIBC index less than the reference values, as compared to controls (26 *vs* 5; p = 0.021) (Table 5).

Finally, it was observed that the presence of IDA resulted in 8.4 fold increased risk of developing FS (Table 6).

Table 4: ***Distribution of cases and controls according to the parameters of iron deficiency anaemia***

Parameters	Cases [N = 35]	Controls [N = 13]	p-value
SI (µg/dl)	45.01 ± 9.85	51.21 ± 7.05	0.044#
TIBC (µg/dl)	444.72 ± 96.90	355.01 ± 95.90	0.006#
SI/TIBC Index (%)	9.72 (7.55 – 16.13)	16.21 (14.49 – 16.73)	0.004*

*SI: Serum iron; TIBC: Total iron binding capacity; Variables with a normal distribution are represented as mean ± SD; Skewed variables presented as median (interquartile range); *Mann-Whitney U test; #Unpaired t-test; p-value <0.05 was considered as statistically significant.*

Table 5: ***Distribution of cases and controls according to the confirmation of iron deficiency anaemia***

Parameters	Criteria	Cases [N = 35]	Controls [N = 13]	p-value
SI (µg/dl)	< 1 year: 40	2	0	0.021*
	> 1 year: 50	24	5	
SI/TIBC Index (%)	< 16	26	5	0.021*
Total		26	5	0.021*

*Non-parametric variables presented as frequency (percentages); *Chi-square test; p-value <0.05 was considered as statistically significant.*

Table 6*: Risk estimate for iron deficiency anaemia and febrile seizures*

Variable	Odd's ratio	95% CI	p-value
IDA [Cases (N = 26) versus Controls (N = 5)]	8.412	2.949, 23.996	< 0.0001

IDA: iron deficiency anaemia; CI: Confidence interval; p-value <0.05 was considered as statistically significant

Discussion

Amongst all the micronutrient deficiencies, iron deficiency is the commonest in the paediatric age group. More importantly, it can be easily corrected and treated. Still, it is observed that, in developing countries, around 46-66% of under-fives children are anaemic. This condition is much worse in India and the 3rd National Family Health Survey (NFHS-3) reported that 70% of under-five children are anaemic[6,14]. IDA is linked to neurological symptoms such as irritability, breath holding spells, impaired cognition, poor school performance, and delay in language development. Additionally, it is also linked to certain morbid conditions such as FS, ischaemic strokes, and pseudo tumour cerebri. Though the role of iron in these conditions is still unclear, some of the contributing factors include abnormal synthesis and metabolism of neurotransmitter, improper myelin formation, and impaired brain energy metabolism. Thus, it is thought iron deficiency may result in change in seizure threshold thus precipitating in the seizures[8].

Principal findings of this study are that 43.3% of the subjects with FS had IDA and as compared to controls, the presence of IDA results in 8.4 times increased chances of FS. However, uncertainty still persist over the role of IDA in FS, with various studies reporting contradictory findings. Findings of this study are supported by Kumar *et al*, who reported higher susceptibility to FS in the cases with iron deficiency[7]. Similar findings are reported by two other different studies[6,15]. In the first study, Sharif *et al* evaluated the relationship between iron deficiency and FS and suggested that a considerable percentage of children with FS had IDA and low SI[15]. In the second study, Chandrashekar *et al.* reported that IDA was found more commonly amongst children with FS as compared to those with febrile illness alone[6]. However, observations of other studies refute the findings of this study. A study by Waheed *et al.* reported that iron concentration is not linked to the development of FS[16]. In another study, Kamalammal *et al.* evaluated the association between IDA and FS in children aged 3 to 60 months and observed that there are no significant differences and rejected the claim that IDA is a triggering factor for FS[17]. Similarly, Bharat *et al.* failed to establish any link between IDA and FS[8]. Kobrinsky *et al.* suggested that iron deficiency may even prevent the development of FS[18]. Following these conflicting results, recent meta-analysis by Kwak *et al.*, reported a clear association between IDA and FS, with an OR of 2.08 to 3.78[19]. Similarly, Nasehi *et al.* had reported an increased incidence of FS in children with IDA (OR = 1.27, 95% CI = 1.03–1.56)[20]. Similar to this study, Aziz *et al*[21] and Jang *et al*[22] performed case control studies in which cases and control were matched for age and gender. However, the latter study reported that the majority of the patients were female. Moreover, as per Leung *et al.* the male-to-female ratio in FS seizures is approximately 1.6 to 1[4]. This is similar to the male-to-female ratio amongst the cases enrolled in this study i.e., 1.4 to 1.

The findings of this study in terms of presenting features (i.e., pallor, pica, and platynychia) are similar to those mentioned in the literature. Kumar *et al.* observed pallor to be the most common sign in children (94%) with IDA. However, platynychia was present in only 5% of the children[23]. Similarly, Soudhabi *et al.* observed that 50% of the children of an orphanage had pallor and 34% had nail changes in the form of platynychia and koilonychias[24]. Studies conducted by Shruti *et al*[25] and Gupta *et al*[26] also reported a statistically significant association between pica and IDA ($p < 0.5$). However, Sadeghzadeh *et al.* did not find any association between pica and anaemia and/or iron deficiency ($p > 0.05$)[27]. This might be because pica is more a cultural behaviour than a result of iron deficiency.

In accordance with Fallah *et al*[28] and Kumar *et al*[29] this study reported a positive family history of FS in cases, however in the study performed Fallah *et al.* this did not reach statistical significance[28]. All studies suggests that family history of seizures could be one strong predisposing factor[30,31]. We could not find any study assessing the role of family history of seizure disorder in patients of FS. However, finding of this study suggest a significant association between the two ($p = 0.012$).

This study observed a significant association between the severity of anaemia and FS ($p<0.0001$). Similarly, Ghosal S, *et al.* observed that significantly greater number of cases with FS had moderate to severe grade of anaemia ($p<0.001$). Moreover, children with moderate to severe anaemia were 6 times more likely to develop FS ($p <0.001$).[32] Similarly, Pisacane *et al.* reported that compared to controls, children with hemoglobin <10 g% had 2.6 times higher risk of developing FS[33]. Thus, severity of the anemia is a risk factor for developing febrile seizures. In this study, compared to controls, cases had significantly lower median Hb, MCV, MCH, and MCHC, but higher median RDW. Similarly, Aziz *et al.* reported significant difference between cases and controls in terms of mean Hb levels ($p = 0.001$) and RDW ($p = 0.004$)[21]. In another study, Srinivasa *et al*. reported low Hb, MCV, and MCHC in febrile fits cases as compared to control (Odd ratio 1.84)[34]. Additionally, Sharawat *et al.* observed that RBC indices showed statistically significant lower mean Hb, MCV, and MCH and higher RDW values in cases compared to controls[35]. However, contrary to the findings of this study, Jang *et al.*, observed no significant difference between the groups in terms of CBC parameters (all p-values >0.05)[22]. This could be due to low prevalence of IDA and improved nutritional status amongst South Korean children. The findings of this study are in accordance with Jang *et al.* who observed a significantly increased TIBC and significantly lower SI levels in cases, as compared to controls[22]. Sharif *et al.* observed a significant difference between cases and controls in the mean SI (p-value = 0.028) and TIBC ($p = 0.0001$). Additionally, the presence of IDA was significantly greater amongst the cases than the controls (45% *vs* 22%; $p = 0.0005$)[15]. Additionally, Sadeghzadeh *et al.* observed that SI: TIBC index < 12% was found in 58% of the cases which was significantly higher than the controls ($p = 0.000035$)[36]. Thus, the findings of this study are similar to those cited in the literature. Since iron deficiency is implicated in the development of FS, its early diagnosis and introduction of iron supplements can help reduce the incidence of FS. Thus, iron status should be routinely checked in children presenting with FS or who are at risk of developing FS.

Conclusions

Children with FS (cases) had lower levels of haematologic parameters such as Hb, MCV, MCH, and MCHC. A family history of FS and a family history of seizure disorders are both risk factors for developing FS in children. Additionally, these children have decreased SI and SI: TIBC index; thus, suggesting an association between FS and IDA. Finally, we conclude that IDA is associated with an increased risk of FS.

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