Original Research Article

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20181554

Iron deficiency anaemia and its association with febrile seizures

Ramesh M. Nigade, Dhairyashil V. Khambalkar*

Department of Paediatrics, D. Y. Patil Medical College and Hospital, Kolhapur, Maharashtra, India

Received: 28 January 2018 Accepted: 28 February 2018

*Correspondence:

Dr. Dhairyashil V. Khambalkar,

E-mail: dhairyashilkhambalkar11@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: As reported by World Health Organization of total world's population about 500 million to 2 billion people are deficient in iron. Iron deficiency is the most common hematological disease found in age group 6 months to 5 years. This age group generally coincides with the age group of occurrences of febrile seizures. Aim of this study was to study the role of iron deficiency in febrile seizures.

Methods: This cross sectional, observational study done in the Pediatrics department of D. Y. Patil Hospital and Research Centre. 170 children of age group between 6months to 5 years will be included in the study over a period of 24 months from May 2015 to May 2017, Presenting with simple and complex febrile seizures to the emergency department and Pediatrics ward of hospital.

Results: In the study the mean age of onset of febrile seizures is 21 months. Severity of anemia doesn't have any correlation with occurrence of febrile seizures. Iron deficient in terms of low HB, low MCH, low MCV, high RDW, low serum Iron, high TIBC and low serum iron and TIBC ratio.

Conclusions: From the current hospital based observational study we have concluded that, iron deficiency anemia was more frequent among children with febrile seizures. The result suggests that iron deficiency anemia may be a risk factor for febrile seizures screening for IDA should be considered in children with febrile seizures. All the investigations (Sr Iron, TIBC) carried out to evaluate iron deficiency anemia were significantly lower. This suggests that iron deficient children are more prone for febrile seizures.

Keywords: Febrile convulsions, Iron deficiency anemia

INTRODUCTION

The World Health Organization estimate iron deficiency anemia is the main cause for anemia; affected population is in between 500 million and 2 billion people across the world. In developing countries Iron deficiency anemia is the most common nutritional deficiency and hematological disease of childhood, mostly between 6months and 24 months of age, 46-66% of all children under 60 months of age are anemic, amongst which almost 50% comprise of iron deficiency. Iron is a nutritional element which is needed for the synthesis of hemoglobin and is also essential for some enzymes that

are involved in neuro-chemical reactions such as myelin formation, brain energy metabolism, neurotransmitters and also for some enzyme metabolism mono-aminoxidase and aldehidoxidase. expression of enzyme cytochrome C oxidase, which is a marker of neuronal metabolic activity is reduced in iron deficiency. So, iron deficiency anemia can alter the seizure threshold of an infant and a child. Neurological symptoms such as poor attention, weak memory, delayed motor developmental and behavioral disturbance caused by iron deficiency anemia are well-known.² Studies have also observed that fever aggravates the negative effects of iron deficiency on the brain: that is iron deficient children may have an increased risk of occurrence of febrile seizures and may also influence the type and duration or recurrence of seizures.³

So, it could be possible that iron deficiency anemia may predispose to other neurological disturbances like irritability, weak memory etc. along with febrile seizures. The observed percentage of febrile seizures is 2 to 4% of all infants and that of recurrence in children with less than 1 year of age is around 50% and 28% for those older than 1 year of age. Majority of the cases of febrile seizure are found to occur in age group 14 to 18 months which directly overlaps with the age group of 6months to 24 months which has a maximum occurrence of iron deficiency anaemia.

A febrile seizure is defined as 'seizures that occur between the age of 6 and 60 months with a temperature of 38 degree centigrade or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures.⁶ Febrile seizures have an excellent outcome. The risk of epilepsy is less than 1%. There is increased morbidity and mortality in febrile seizures due to aspiration and hypoxia caused due to prolonged episodes.⁷

Many studies have been conducted in order to study the relation between iron deficiency anemia and febrile seizures. Many studies show positive outcome while many studies show that there is no relation between iron deficiency anemia and febrile seizures so there is need to explore this topic ahead and have some firm outcome for the same.

Objectives of this study were to find out the relation between iron deficiency anemia and febrile seizure, find out the most common age for occurrence of febrile seizures and find out relation between severity of Iron deficiency anemia and febrile seizures.

METHODS

A Hospital based cross-sectional observational study were conducted on 170 children of age group between 6 months to 5 years will be included in the study over a period of 24 months between May 2015 to May 2017, presenting with simple and complex febrile seizures to the emergency department and Pediatrics ward of Dr. D. Y. Patil Hospital. The sample size was calculated in percentage of iron deficiency in febrile seizure.

Data collection

Children with febrile seizures between 6 months to 5 years brought to Dr. D. Y. Patil Hospital and treated on OPD or IPD basis, depending upon the general condition. Emergency treatment will be given to stabilize the patient. Parents will be then asked for permission of their children to participate in the study.

After informed consent, detailed history will be taken, and physical examination will be done, then venous blood sample will be collected and sent to the pathology department for investigation. To diagnose iron deficiency following investigation will be done, which include, Hemoglobin estimation (Hb), RBC count, peripheral smear, MCV, MCH, MCHC, Red cell distribution width (RDW), Sr. iron, Total iron binding capacity (TIBC), Sr. Iron:TIBC ratio.

Equipment are used Nihon Kohden cell tac used for CBC and Fi_{mens} Dead_{max} used for Sr. iron and TIBC.

Results of the investigation will be correlated with the patient. Anemia is defined as Hemoglobin concentration <11g/dl. Microcytosis is defined as MCV below the age corrected normal values for erythrocytic volumes (MCV of 70 fl/mcl in children <2 years, of 73fl/mcl in children 2-4 years, 75 fl/mcl in children5-7 yrs).

Inclusion criteria

- Children of age group 6 months to 5 years who come to with febrile seizure.
- Seizures associated with fever.
- Child is otherwise neurologically healthy without any neurological abnormality before and after episode of seizure.

Exclusion criteria

- Age group < 6 months and >5 years.
- Afebrile seizure.
- Known case of epilepsy.
- Those having any signs of central nervous system infection.
- Those with any neurodevelopmental problem (cerebral palsy, prematurity, hemiplegia, neurodegenerative disorder).
- Those who were previously diagnosed cases of other hematologic problems (Thalassemia, sickle cell anaemia, haemophilia), bleeding or coagulation disorder, haematological malignancy.
- Those who are on iron supplementation.

RESULTS

Table 1 shows gender distribution of children. The percentage of male patients involved in the study is 71.8% which is higher than that of female patients involved in the study which is only 28.2%.

Table 1: Gender distribution of children.

Gender	No. of children	%
Female	48	28.2
Male	122	71.8
Total	170	100.0

Table 2 shows that the percentage of the children chosen for the study between the age group of 6 months to 12 months is higher which is 32.9% than the percentage of children between the other age groups as 13-18 months, 19-24 months, 25-30 months, 30-60 months which are 8.2%, 20%, 12.9%, 24.7% respectively. Mean age of the children involved in the study is 21 months.

Table 2: Age in month's distribution of children.

Age in months	No. of children	%
6-12	56	32.9
13-18	14	8.2
19-24	34	20.0
25-30	22	12.9
30-60	42	24.7
Total	170	100.0

Mean±SD: 21.73±9.91

Table 3: Fever distribution of children.

Fever	No. of children	%
<100 °F	88	51.8
100-101 °F	32	18.8
>101 °F	50	29.4
Total	170	100.0

Mean±SD: 99.97±1.12

Table 3 shows that 51.8% patients had body temperature between <1000 F which is more than the patients who had body temperature of 100-1010F which is 18.8% and patients with body temperature of >1010F are 29.4%

Table 4: Hemoglobin distribution of children.

Hemoglobin (g/dl)	No. of children	0/0
6-7	6	3.5
7-8	6	3.5
8-9	22	12.9
9-10	42	24.7
10-11	44	25.9
>11	50	29.4
Total	170	100.0

Table 5: MCV/MCH and MCHC distribution of children.

	No. of children	%
MCV		
< 70	60	35.3
70-80	106	62.3
>80	4	2.4
MCH		
<25	72	42.4
25-30	94	55.3
>30	4	2.4
MCHC		
<30	42	24.7
30-35	126	74.1
>35	2	1.2

Mean MCV is 71.98fl, Mean MCH is 24.6, Mean MCHC is 30.74, p value <0.001

Table 4 shows haemoglobin distribution of children. It shows that <11 is considered as anemic which comprise of 70.6% of which 6-7gm%, 7-8gm%, 8-9gm%, 9-10gm%, 10-11gm% includes 3.5, 3.5, 12.9, 24.7, 25.9 respectively.

Patients with MCV <80fl comprised of 97.6% among it <70fl are 35.3% and between 70-80fl is 62.3% and patients with >80fl are much low which comprise of only 2.4

The mean MCV was 71.98fl, the value of MCH among patients in thesis <25 are 42.4% and between 25-30 is 55.3% and >30 is 2.4%.

The mean MCH was 24.6, the value of MCHC <30 among the patients of study comprised of 24.7%, 30-35 comprised of 74.1% and >35 is about 1.2%, the mean MCHC was 30.74.

Table 6: Serum iron distribution of children.

Serum iron	No. of children	%
< 50	40	23.5
50-90	106	62.4
>90	24	14.1

p value<0.001

Serum ferritin level <90 comprise of 85.9 % of patients among which <50 are 23% and between 50-90 are 62.4%. And the patients with >90 are only 14.1%. The p value is significant for serum ferritin level for this study.

Table 7: Febrile seizures and its association with or without iron deficiency.

	No. of patients	Percentage
Febrile seizure with iron deficiency	146	85.88
Febrile seizure without iron deficiency	24	14.12
	170	100

P value< 0.001

Patients with febrile seizures and having iron deficiency account for about 85.88% of all the patients in this study and the patients with febrile seizures with no iron deficiency account for 14.12%. p value is significant for this study.

Table 8: TIBC distribution among patients.

TIBC	Frequency	Percentage
Raised	108	64.4
Normal	62	35.6
Total	170	100

In this study patients with raised TIBC comprise of 108 patients which are about 64.4% and normal TIBC is about 35.6%. P Value is significant for TIBC value for this study.

Table 9: Serum Iron / TIBC.

Serum Iron/TIBC	No.	0/0
<10	42	24.7
10-20	114	67.1
>20	14	8.2

p value < 0.001

Table 9 shows that the Serum Iron/TIBC <20 accounts for about 91.8% of which <10 are24.7% and 10-20are 67.1% and p value is significant for this study.

Table 10: Peripheral smear distribution of children.

Peripheral smear	No. of children	%
Normocytic norm chromic	56	32.9
Hypochromic microcytic	114	67.1
Total	170	100.0

In this study, patients with hypochromic microcytic peripheral smear are 114 which are about 67% and normocytic normochromic are 56 which are 33%. Student t test (two tailed, independent) has been used to find the significance of study.

DISCUSSION

In present study there was a preponderance of male gender in for the febrile seizure group which is around 2.5:1 for male as to female. Many studies have been conducted since long time which always showed that boys have consistently emerged with a higher frequency of febrile seizures. Ratios of boys: girls in different studies have ranged from 1.1:1 (Nelson and Ellenberg) to 2:1; (Hauser; Forsgren et al).^{8,9} However, findings of our present study are in contrast to other large studies done by Verity et al, 1985 who found that there is no sex difference in occurrence of febrile seizures. A study done by NCPP showed that there is a male predilection only among black population (Nelson and Ellenberg). However, whether if there is any biological basis for the gender-specific differences in occurrence of febrile seizure, or whether boys just contract more fevers due to their outdoor lifestyle and therefore are at greater risk, that is currently not established.¹⁰

The mean age of occurrence of febrile seizures in present study was about 21 months which was comparable to the other studies such as Alfredo Piscane et al found that the mean age for febrile seizures was about 15 months. ¹¹ Separate studies done by Vasvani RK et al, Waruiru C et al and Azhar S Daoud et al also found that febrile seizure peaks at 18 months. ¹²⁻¹⁴ Ellenberg et al found the average seizure age to be 23.3 months. Generally, it is noted that noted that the most common age in which the febrile

seizure and the first febrile seizure occur is second year of life.

Besides mean age of febrile seizures, many of the studies have demonstrated young age as a risk factor for complex febrile seizure e.g. Wallace et al, Al- Eissa et al, Farwell et al. ¹⁵⁻¹⁷ Young age at onset of febrile seizure is also been associated with its recurrence Uhari et al, the analysis of which was not done in present study. ¹⁸

The axillary temperature taken at the time of admission, before prescribing anti pyretic as recorded by standard protocol. In present study, initial temperature of the body was around, 100° F. In the literature, the higher the peak temperature, the lower the chance of recurrence suggested by Berg et al, what was not established in present study. A tentative explanation could be the initial anti-pyretic usage which was unknown in the present study and measurement of admission temperature than height of temperature, which was beyond the scope.

In present study patients having no past history of febrile seizures are 116 patients out of 170 that is around 68% i.e. around 68% of patients didn't had past history of febrile seizures which in contrary was observed in study by Wallace et al in study 34 patients out of 72 i.e. around 47% had past history of febrile seizures.

In present study family history is not significant as more patients are from non-consanguineous marriage. Studies done by Azhar S Daoud et al and Khalid N et al found family history of febrile seizures and family history of epilepsy were higher in cases than controls, the difference was not statistically significant. While other studies by Farwell et al, (29%) proved that there is a strong family history association, much greater than what reported by Lewis et al (11%).

According to Millichap et al both febrile and afebrile seizures are common in families of febrile seizures children.¹⁹

In present study 162 patients had normal developmental history which is about 94% which are comparable to studies done by Ellenberg JH which shows 82% of patients with normal developmental history.

Iron deficiency

A set of analysis for Iron deficiency as a risk factor for febrile seizure was done in the present study, results of which were obtained by biochemical and haematological investigations. Diagnostic threshold that was employed in present study for Iron deficiency were Hb level <11g/dl, Among the RBC indices MCV <80 fl, MCH <30pg, MCHC <12gm/dl, RDW >14%, Sr. iron <90 μ g/dl, TIBC >500mcg/dl and Sr. iron (TIBC <20).

Many enzymes require iron as a cofactor for their reaction, it also has a major role in functioning of some

neurotransmitters, in DNA replication and some functions of hormone. Therefore, deficiency in iron may lead to organ dysfunction and disruption of normal cells.

Most common consequence of iron deficiency is anemia, but it may also present as manifestations such as both cognitive and behavioral changes, impaired physical growth and also impairment of immune system.

In present study red blood indices mean Hb, MCV and MCH was 10.35g%, 71.98 fl, 24.6 pg respectively which was significantly low. Kumari PL et al, Naveed-ur-Rehmann et al and Piscane et al had results similar to present study while Azhar S Daoud et al, Vasvani et al failed to find any significant difference between the two groups. ²⁰

Serum iron and iron saturation percentage

The balance between iron entering the circulation and leaving circulation is given by serum iron concentration. As a measure of iron deficiency, serum iron estimation can have some limitations because iron has a very wide range of normal values that can vary significantly with age, sex, laboratory methodology. There can be circadian changes (as much as $100\mu\text{g/dl}$ during the day) in iron level and finally serum Iron levels can fall even in mild or transient infection.

In present study shows that there was significantly low iron level which was <90mcg/dl in about 86%. Present study also suggests that about 86 percent children having iron deficiency had febrile seizure. Pisacane et al studied the serum iron level between 6 - 24 months of age, where the level was low in febrile children. Bidabadi et al reported that the serum Iron level in febrile seizure was higher at a statistically insignificant level. Khalid N et al couldn't appreciate significant TIBC changes between cases and controls.²¹

CONCLUSION

There had been many studies conducted regarding association between iron deficiency anemia and febrile seizures, but the results are inconclusive and so this study was conducted to see whether there is any association between iron deficiency anemia and febrile seizures.

From the current hospital based observational study we have concluded that males are having more incidence of febrile seizures than females. Mean age for occurrence of febrile seizures is 21 months. Iron deficiency anemia was more frequent among children with febrile seizures.

The result suggests that iron deficiency anemia may be a risk factor for febrile seizures Screening for IDA should be considered in children with febrile seizure. All the investigations (Sr. Iron, TIBC) carried out to evaluate iron deficiency anemia were significantly lower. This suggests that iron deficient children are more prone for febrile seizures.

Funding: No funding sources Conflict of interest: None declared

Ethical approval: The study was approved by the

Institutional Ethics Committee

REFERENCES

- McLean E, Cogswell M, Egli I, Wojdyla D, De Benoist B. Worldwide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 1993–2005. Public health nutrition. 2009 Apr;12(4):444-54.
- Halliwell B. Oxidative stress and neurodegeneration: where are we now?. J Neurochem. 2006 Jun 1;97(6):1634-58.
- 3. Idro R, Gwer S, Williams TN, Otieno T, Uyoga S, Fegan G, et al. Iron deficiency and acute seizures: results from children living in rural Kenya and a meta-analysis. PLoS One. 2010;5(11):e14001.
- Shinnar S, Berg AT, Moshe SL, O'dell C, Alemany M, Newstein D, et al. The risk of seizure recurrence after a first unprovoked afebrile seizure in childhood: an extended follow-up. Pediatr. 1996 Aug 1;98(2):216-25.
- Derakhshanfar H, Abaskhanian A, Alimohammadi H, ModanlooKordi M. Association between iron deficiency anaemia and febrile seizure in children. Med Glas (Zenica). 2012 Aug 1;9(2):239-42.
- Fallah R, Sabbaghzadegan S, Karbasi SA, Binesh F. Efficacy of zinc sulfate supplement on febrile seizure recurrence prevention in children with normal serum zinc level: A randomised clinical trial. Nutrition. 2015;31(11):1358-61.
- Van-Landingham KE, Heinz ER, Cavazos JE, Lewis DV. Magnetic resonance imaging evidence of hippocampal injury after prolonged focal febrile seizures. Ann Neurol. 1998;43(4):413-26.
- 8. Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. Pediatr. 1978;61(5):720-7.
- 9. Forsgren L, Sidenvall R, Blomquist HK, Heijbel J. A prospective incidence study of febrile seizures. Acta Paediatrica. 1990;79(5):550-7.
- 10. Verity CM, Golding J. Risk of epilepsy after febrile seizures: a national cohort study. BMJ. 1991;303(6814):1373-6.
- 11. Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'apuzzo A, et al. Iron deficiency anaemia and febrile seizures: case-control study in children under 2 years. BMJ. 1996;313(7053):343-4.
- 12. Vaswani RK, Dharaskar PG, Kulkarni S, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. Indian Pediatr. 2010;47(5):437-9.
- 13. Waruiru C, Appleton R. Febrile seizures: an update. Archives of Disease in childhood. 2004;89(8):751-6.

- Daoud AS, Batieha A, Abu-Ekteish F, Gharaibeh N, Ajlouni S, Hijazi S. Iron status: a possible risk factor for the first febrile seizure. Epilepsia. 2002;43(7):740-3.
- 15. Wallace RH, Scheffer IE, Barnett S, Richards M, Dibbens L, Desai RR, et al. Neuronal sodium-channel α1-subunit mutations in generalized epilepsy with febrile seizures plus. The American Journal of Human Genetics. 2001;68(4):859-65.
- 16. Al-Eissa YA. Febrile seizures: rate and risk factors of recurrence. J Child Neurol. 1995 Jul;10(4):315-9.
- Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures effects on intelligence and on seizure recurrence. New England J Med. 1990;322(6):364-9.
- 18. Uhari M, Rantala H, Vainionpää L, Kurttila R. Effect of acetaminophen and of low intermittent

- doses of diazepam on prevention of recurrences of febrile seizures. J Pediatr. 1995;126(6):991-5.
- 19. Millichap JG, Millichap JJ. Role of viral infections in the etiology of febrile seizures. Pediatric Neurol. 2006;35(3):165-72.
- 20. Kumari PL, Nair MK, Nair SM, Kailas L, Geetha S. Iron deficiency as a risk factor for simple febrile seizures-a case control study. Indian Pediatr. 2012;49(1):17-9.
- 21. Bidabadi E, Mashouf M. Association between iron deficiency anaemia and first febrile seizure: a case—control study. Seizure. 2009;18(5):347-51.

Cite this article as: Nigade RM, Khambalkar DV. Iron deficiency anaemia and its association with febrile seizures. Int J Contemp Pediatr 2018;5:1120-5.