Research Article

Iron deficiency as a risk factor for febrile seizures

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Abstract

Introduction: Febrile seizures (FS) are a form of acute symptomatic seizures. Iron deficiency Anaemia (IDA) is one of the most common nutrition related problems in the world. Iron is important for neurological functions and development of brain. **Methods:** A case control study was done among 100 children at the Pediatric department, NRI Medical College & Hospital. Total of 100 children between age group of 6 months – 6 years with fever were included, out of which 50 children with first febrile seizure were enrolled as cases. 50 children with fever without seizure were enrolled as control group. A pre designed proforma was used to collect the relevant information. Blood samples collected from all cases and control groups and estimated for hematological parameters. **Results**: The mean age in months was 22.4 among cases and 26.7 months in controls. Nine cases had a positive family history of febrile seizures. Respiratory tract infections were most common underlying cause of illness. The mean and standard deviation values of all the hematological parameters (HB, PCV, MCV, MCH, MCHC & serum Ferritin) showed that measurements were lower among cases compared to control and it was statistically significant. **Conclusions**: IDA was more frequent among children with FS than those with febrile illness alone. The result suggests that IDA may be a risk factor for FS. Screening for IDA should be considered in children with First Febrile Seizures (FFS).

Keywords: Febrile seizures, Iron deficiency anaemia, Hematological parameters, Case control study

Introduction

Febrile seizures (FS) are a form of acute symptomatic seizures. They occur in 2% to 5% of children and are the most common form of childhood seizures. In the past, it was believed that most FS represented a form of epilepsy and that prognosis was not favorable [1]. Febrile seizure episodes are agonizing to the parent and child and can cause psychological trauma to both.

Over the past 25 years much more information on febrile seizures has accumulated and the prognosis for febrile seizures has been found to be excellent. Such seizures are not associated with detectable brain damage and epilepsy will eventually develop in only a small minority of children who had FS. A Febrile Seizure is defined by the International League Against Epilepsy (ILAE) as a "Seizure occurring in childhood after l month of age associated with a febrile illness not caused by an infection of central nervous system ,without previous neonatal seizure or a previous unprovoked seizure and not meeting the criteria for other acute symptomatic seizure" [2].

The febrile illness must include a body temperature of greater than 38.4 0C, although the increased temperature may not occur until after the seizure. Febrile seizures are age dependent and are common between ages 6 months and 6 years. Febrile seizures can be simple or complex.

Simple febrile seizures are generalized seizures lasting less than 15 minutes, not recurring within the febrile episode and with no post ictal neurological abnormalities. Complex febrile seizures are focal seizures lasting for more than 15 minutes, recurring within febrile episode and associated with post ictal neurological abnormalities including Todd paresis.

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Most febrile seizures are simple (80%). Most are short lasting with 78% less than 6 minutes and 50% less than 3minutes. Febrile status is seizure duration of 30 minutes about 5% of FS last for 30 minutes. FS are mostly generalized tonic clonic seizures may be partial in complex febrile seizures. A strong family history of febrile seizures in siblings and parents suggests a genetic predisposition [3].

Iron deficiency Anaemia (IDA) is one of the most common nutrition related problems in the world. In developing countries 46-66% of under fives are anemic. In India as per NFHS-3 70% of under fives are anemic. Iron is important for neurological functions and development of brain [4].

Considering the age prevalence of IDA and FS which are the same the role of iron in the metabolism of neurotransmitters(such as GABA dopamine and Serotonin) [5] and some enzymes such as monoaminooxidase, the function of hemoglobin in carrying oxygen to the brain and fever can exacerbate symptoms that result from anemia, a relationship between IDA and FS is probable. Iron deficiency is postulated as a risk factor for febrile seizures in children and it is an easily correctable condition [6,7].

Iron is an important component of cellular metabolism of every organ. A number of neurological manifestations have been recognized with iron deficiency anemia. Subtle dysfunction includes impaired cognition, poor scholastic performance, irritability, language developmental delay, breath holding spells.

Morbid dysfunction includes ischemic strokes, venous thrombosis, pseudo tumor cerebri and febrile seizures. The biological basis for this is not completely understood, but possibilities include abnormalities in neuro transmitter metabolism, decreased myelin formation and abnormalities in brain energy metabolism. Iron deficiency may alter the seizure threshold [8,9].

Present study which has been done in a tertiary care hospital with an objective to evaluate the association between iron deficiency anaemia and first febrile seizure

Material & Methods

Study design: Case control study
Study setting: Pediatric department, NRI Medical College & Hospital
Study period: August 2014 – July 2015

Inclusion criteria

Total of 100 children between age group of 6 months – 6 years with fever were included, out of which 50 children with first febrile seizure were enrolled as cases. 50 children with fever without seizure were enrolled as control group.

Exclusion criteria

Recurrent seizures not precipitated by fever
Seizures associated with intracranial infections
Developmental delay and neurological deficits
Metabolic Seizures

Methods

A pre designed proforma was used to collect the relevant information. Details of age, sex, developmental milestones, family history of febrile seizure, epilepsy, peak temperature, underlying illness and clinical examinations were recorded for cases and control groups.

Details of seizure type, duration, frequency were recorded and classified as simple and complex febrile seizures and investigated. Blood samples collected from all cases and control groups and estimated for iron deficiency. RBC indices and hemoglobin estimation by automatic cell counter technique. Serum ferritin was measured by chemiluminescent method.

Statistical data was analyzed by using SPSS package and Z-test was used for checking the significance with $p < 0.05$ considered as statistically significant.

Results

Among the total 100 cases, 50 were cases with first febrile seizure and other 50 were controls. The mean age in months was 22.4 among cases and 26.7 months in controls. With regards to family history of febrile seizures, 9 cases had positive history among cases and only 3 cases in controls. Family history of epilepsy was seen among 2 & 1 in cases and controls respectively (Table 1).

Table No 1: Demographic characteristics, peak temperature on admission, and underlying cause of illnesses among cases of First Febrile Seizure (FFS) and controls.

Characteristics	First Febrile Seizure (FFS) CASES (N=50)	Controls (N=50)
Temperature peak on admission in centigrade	38.9	38.6
Mean Age in months	22.4	26.7
Family H/o. Febrile seizures	9	3
Family H/o. epilepsy	2	1
Underlying cause of illness		
Respiratory tract infections	23	19
Gastroenteritis	9	13
Urinary tract infections	10	11
Non specific underlying causes	8	7

Table-2: Mean levels of HB, PCV, MCV, MCH, MCHC and Serum Ferritin among cases with FFS and controls.

Blood Indices	FFS CASES (n=50)		Controls (n=50)		p value*
	Mean	SD	Mean	SD	
Hb /gm/lts	10.9	1.36	12	1.74	<0.05
Packed Cell Volume (PCV)	32.9	3.31	35.7	4.5	<0.05
Mean corpuscular volume (MCV) (fl)	69.4	3.63	74.42	5.64	<0.05
Mean corpuscular hemoglobin (MCH) (pg)	24.81	4.30	28.2	3.61	<0.05
Mean corpuscular hemoglobin concentration (MCHC)	31.5	1.36	33.5	1.70	<0.05
S.Ferritin(ng/ml)	18.26	8.33	49.32	32.62	<0.05

*p<0.05 considered statistically significant

Table-3: The number of children with low levels of HB, PCV, MCV, MCH and S.FERRITIN among cases with FFS and controls

Blood Indices	Cases	Percentage (%)	Controls	Percentage (%)
HB g/l <11	33	66	13	26
PCV <35	33	66	19	38
MCV <70	28	56	14	28
MCH pg <25	29	58	15	30
MCHC <32	26	54	10	20
S.FERRITIN ng/ml <15	30	60	14	28

p value is significant <0.05 in cases when compared to controls in all the parameters mentioned above

Underlying cause of illness: With regards to underlying cause of illness, respiratory tract infections was most common (46%), followed by urinary tract infections (20%), gastroenteritis (18%).

Hematological parameters including HB, PCV, MCV, MCH, MCHC & serum Ferritin were measured among cases and controls. The mean and standard deviation values of the parameters showed that measurements were lower among cases compared to controls. And the difference between cases and controls was statistically significant (p<0.05) among all the hematological parameters (Table 2).

Total number of children with low levels of hematological parameters was measured among cases and controls. Hemoglobin level was less than 11 gm% in 66% of cases and only 26% among controls. Packed Cell Volume (PCV) was less than 35 among 66% of cases and 38% of controls. Mean corpuscular volume (MCV) was less than 70 fl in 56% of cases and 28% in controls. 58% of cases and 30% of controls had Mean corpuscular hemoglobin (MCH) less than 25 pg. Mean corpuscular hemoglobin concentration (MCHC) less than 32 in 54% of cases and 20% of controls. S. Ferritin was less than 15 ng/ml in 60% and 28% among cases and controls respectively. All the parameters were lower among cases compared with controls which was found to be statistically significant ($p<0.05$) (Table 3).

Discussion

Present hospital based study found that the mean age in months was 22.4 among cases and 26.7 months in controls. Nine cases had a positive family history of febrile seizures. Respiratory tract infections were most common underlying cause of illness. The mean and standard deviation values of all the hematological parameters (HB, PCV, MCV, MCH, MCHC & serum Ferritin) showed that measurements were lower among cases compared to control and it was statistically significant. Similar results were obtained by Dawn et al [10] where children with febrile seizures almost twice likely to have iron deficiency compared to controls.

All the parameters were lower among cases compared with controls which was found to be statistically significant ($p<0.05$) with similar kind of findings noticed in Daoud, et al [11]., the significance of iron status as a possible risk factor was evaluated and The mean serum ferritin level in the cases was 29.5 mcg/L, much lower than the values in the controls (53.5 mcg/L). Also similar observations were made in a study done by Rajwanti, et al [12] from Mumbai where the mean serum ferritin level was significantly low in children with first febrile seizures (31.9±31.0 mcg/L) as compared to controls (53.9±56.5 mcg/L) (P=0.003).

Yousefichaijan P et al on the relationship between iron deficiency anaemia and simple febrile convulsion in children observed that the prevalence of anemia in the group with febrile convulsion was significantly less than that in the control group: 22.5% of the children in the group with febrile convulsion and 34% in the control group exhibited anemia ($P < 0.001$). Moreover, the group with febrile convulsion had significantly higher blood indices, such as Hb, Hct, MCV, MCH, and MCHC, compared to the control group ($P < 0.001$) [13].

Another similar kind of study by PL Kumari et al in Kerala observed a highly significant association between iron deficiency and simple febrile seizures in both univariate and multivariate analysis. Crude odds ratio was 5.34 (CI 3.27- 8.73, P<0.001) and adjusted odds ratio in the logistic regression analysis was 4.5 (CI 2.69- 7.53, P<0.001) [14]. A case control study by Boshra A.T. Ahmed on iron deficiency as a risk factor for simple febrile seizures found that Non significant differences between the cases and the control group in terms of age, temperature, sex, ESR, WBC, RBC, MCV, MCHC and platelets. The mean Hb, HCT, serum ferritin, serum iron, and MCH were significantly low in children with first febrile seizures as compared to controls [15].

Conclusion

The association between iron deficiency anemia and febrile seizures has been studied before without any conclusive reports and this study was done for further confirmation. None the less, selection bias as well as confounding by social class does not seem likely in this study. IDA was more frequent among children with FS than those with febrile illness alone. The result suggests that IDA may be a risk factor for FS. Screening for IDA should be considered in children with FFS.

Fever can worsen the negative effect of anemia of iron deficiency on the brain and a seizure can occur as a consequence. Alternatively, anemia can be associated with the severity of a febrile illness, and more severe cases could be more likely to get seizures. All the investigations carried out to evaluate iron deficiency anemia were significantly lower in cases as compared to controls. This suggests that iron deficient children are more prone for febrile seizures.

A follow up study of patients found to be iron deficient at the time of first febrile seizure to determine the incidence of subsequent febrile seizures after treatment for iron deficiency would be of great interest.

Recommendations

1. All Children in the age group of 6 months to 6 years with iron deficiency and family history of febrile seizure, epilepsy should be supplemented with iron to decrease the incidence of febrile seizure

2. All children in the age group of 6 months to 6 years should be evaluated for early detection of iron deficiency both clinically and biochemically and plan for early iron supplementation to prevent febrile seizures.
3. Iron supplementation is very cost effective and will go a long way in decreasing the incidence of febrile seizures and correction of Iron deficiency anemia.

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Permission of IRB: Yes

References

1. Johnston MV. Seizures in childhood. In: Kleigman RM,Behrman RE,Jenson HB, Stanton BP. Nelson Text Book of Pediatrics 18th Edition Philadelphia: Saunders Elsevier; 2007. p.2457-8.

2. Commission on Epidemiology and Prognosis, international league against epilepsy. Guidelines for epidemiologic studies on epilepsy.Epilepsia1993;34:592.

3. Nakayama J, Hamano K, Iwasaki N, Nakahara S, Horigome Y, Saitoh H, Aoki T, Maki T, Kikuchi M, Migita T, Ohto T, Yokouchi Y, Tanaka R, Hasegawa M, Matsui A, Hamaguchi H, Arinami T. Significant evidence for linkage of febrile seizures to chromosome 5q14-q15. Hum Mol Genet. 2000 Jan 1;9(1):87-91.

4. World Health Organization. Iron Deficiency Anemia. Assessment, Prevention and Control. A Guide for Program Managers. WHO/NHD/013;Geneva: 2001.

5. Beard J. Iron deficiency alters brain development and functioning. J Nutr. 2003 May;133(5 Suppl 1):1468S-72S.

6. Wike WM, Kiser WR. Iron deficiency anaemia and febrile convulsions. Possible confounding factors include lead toxicity.... BMJ. 1996 Nov 9;313(7066):1205.

7.Prasad AN, Seshia SS. Susceptibility to febrile seizures: more than just a faulty thermostat! Can J Neurol Sci. 2009 May;36(3):277-9.

8. Batra J, Seth PK. Effect of iron deficiency on developing rat brain. Indian J Clin Biochem. 2002 Jul;17(2):108-14. doi: 10.1007/BF02867982.

9. Yager JY, Hartfield DS. Neurologic manifestations of iron deficiency in childhood. Pediatr Neurol. 2002 Aug;27(2):85-92.

10. Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, Craig WR. Clin Pediatr (Phila). 2009 May;48(4):420-6. doi: 10.1177/0009922809331800. Epub 2009 Feb 19.

11. 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 Jul;43(7):740-3.

12. Vaswani RK, Dharaskar PG, Kulkarni S, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. Indian Pediatr. 2010 May;47(5):437-9. Epub 2009 Sep 3.

13. Yousefichaijan P, Eghbali A, Rafeie M, Sharafkhah M, Zolfi M, Firouzifar M. The relationship between iron deficiency anemia and simple febrile convulsion in children. J Pediatr Neurosci. 2014 May;9(2):110-4. doi: 10.4103/1817-1745.139276.

14. 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 Jan;49(1):17-9. Epub 2011 May 30.

15. Boshra A.T. Ahmed. Iron Deficiency as a Risk Factor for Simple Febrile Seizures. Med. J. Cairo Univ. 2013; 81 (2):51-54.

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