Iron Deficiency Anemia & Febrile Seizures case- Control Study in Children Under 5years

Abdul-Kareem M. Ali

CABP

Abstract: A case control study is done on children aged 6mo - 5years attained Tikrit Teaching Hospital and Beji General Hospital during the period from the 1st January to the end of December 2005. To investigate the association between iron deficiency anemia and febrile seizures.

Methods: Measures of iron sufficiency including hemoglobin concentration (HB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and plasma ferritin (PF), were measured in 100 children with febrile seizure and compared with 100 controls matched for age and sex with febrile illnesses without convulsions.

Results: The study showed a preponderance of males with febrile seizures, and male to female ratio was (1.5: 1) while in controls male to female ratio was (1.27: 1). Mean ferritin level was significantly lower in cases with febrile seizure (29.5 ± 21.3 µg/L) than in controls (53.3 ± 37.6 µg/L) with p = 0.0001. The proportion of subjects with a PF level ≤30 µg/L was significantly higher among children with FS (66 of 100 vs. 32 of 100) than in controls (p = 0.000). Mean level of Hb, MCV, and MCH also were lower among FS cases, but differences failed to attain statistical significance. A higher proportion of cases with FS had an HB < 110 g/L, MCV< 72 fL, and MCH < 24 pg than did the controls, but the differences were not statistically significant. There were no statistically significant differences between the cases and the controls in the mean peak temperature on admission, types of underlying illness, or family history of epilepsy and of febrile convulsion.

Conclusions: PF level was significantly lower in children with FS than in the control group, suggesting a possible role for iron insufficiency in FS.

Key words: Iron status – febrile seizure.

Introduction

Febrile seizures (FSs) are the most common type of seizers, occurring in 2-5% of all children [1]. FS was defined as an event in infancy or childhood, usually occurring between 5 months and 6 years, associated with fever but without evidence of intracranial infection or other defined causes of seizures. A single seizure of < 15 min duration in the presence of fever without focal features was defined as a single FS, whereas, seizures were defined as complex if they last > 15 min, had focal features, or occurred more than once in 24 h [8]. Because of their association with later epilepsy, recent studies have attempted to identify their risk factors [2,3], including family history of febrile convulsions or epilepsy, perinatal factors, features of the acute underlying illnesses accompanying the FS, and the temperature peak. Pisacane et al. [4] reported that anemia was more common in children younger than 2 years with febrile seizures (FSs), whereas, in contrast, Kobrinsky et al. [5] reported that iron deficiency raises the threshold for seizures. Iron is involved in the metabolism of several neurotrasmitters, and monoamine and aldehyde oxidases are reduced in iron- deficiency anemia [6], which common during the second and third years of life, and have variably been associated with behavioral and developmental disturbances [7]. The aim of the study is to focus on the assessment of the relation, if any, of iron status with FS.

Methods& Patients:

Children with febrile seizure (FS) admitted to the Departments of pediatrics, Tikrit Teaching Hospital and Beji General Hospital during the period from 1st of January to the end of December 2005 were included in the study. Children with a history of seizures, central nervous system (CNS) infections, developmental delay, and/ or neurologic deficit were excluded from the study. Total of100 children (60 male and 40 female) with FS were enrolled in this study. A reference group (100) was selected from children hospitalized for a febrile illness (such as upper and lower respiratory tract infections and gastroenteritis) but without seizures. Controls were group-matched to cases on age (within 1 month for children younger than 1 year, and 2 months for children older than 1 year) and sex. Residents who did not know the hypothesis of the study randomly selected a similar number of eligible controls for each group of cases. The process of control selection was carried out every 2-3 days, depending on the number of hospitalized cases. Eighty- eight children had simple and twelve had complex FS. An informed consent was obtained from parents or legal guardians.

Age, sex, developmental milestone, family history of FSs or epilepsy, mean of temperature peak at admission, and the underlying illness were recorded for all cases and controls, as well as details of the seizure

history, duration, frequency, and focality for cases with FS. Blood samples were collected from all participants for hemoglobin (HB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and plasma ferritin (PF). HB, MCV, and MCH were part of a complete blood count with 18 parameters (Cobas, Micros, Roche). PF level was measured by using the IMx ferritin assay in a microparticle enzyme immunoassay (MEIA) for quantitative determination of human PF [9].

Cases and controls were compared as regards HB, MCV, MCH, and PF both as continuous and as dichotomous variables. The x^2 test was used to assess the statistical significance of the differences in proportions, whereas the two- sample *t* test was used when the data were treated as continuous.

Results:

The results are based on 100 children with FS and a reference group of 100. Febrile seizures occurred more in males (60/100) than females (40/100) with a ratio 1.5: 1, while in controls, males (56/100) were more affected than females (44/100) with a ratio of 1.27: 1 and as shown in the Table1.

Age, family history of febrile convulsion or epilepsy, the mean temperature peak on admission, and underlying illnesses among cases and controls are detailed in table 2.

Table 1. Gender distribution in children with febrile seizures and controls

Groups	Male	Female
Febrile convulsion (n = 100)	**60 (60%)**	**4o (40%)**
Controls (n = 100)	**56 (56%)**	**44 (44%)**

Table 2. The demographic characteristic, peak temperature on admission, and underlying causes of illness among cases of FS and controls

Characteristic	FS cases (n = 100)	Controls (n= 100)
Temperature peak on admission in c◦ (mean)	38.9	38.6
Age in months (mean)	18.8	19.1
Family history of FS	12	4
Family history of epilepsy	3	1
Respiratory tract infections	57	61
Gastroenteritis	35	32
Nonspecific underlying illness	8	7

FS, febrile seizure

Table 3 shows that the mean PF level was significantly lower (p = 0.0001) in the FS group compared with the reference group. HB, MCV, and MCH levels were also lower in the cases, but differences were not statistically significant.

As shown in Table 4, the proportion of cases with a PF ≤ 30 μg/L was significantly

higher (p= 0.000) among the cases with FS than in controls. The proportions of cases with a HB < 110 G/L, MCV <72 fL, and MCH, 24 µg/L were also higher among cases than controls, but differences were not statistically significant. The mean levels of HB (97.2), MCV (70.7), MCH (22.9), and PF (22.2) were lower in children with complex than simple febrile seizures, but differences were statistically significant in HB and MCH. Failure to attain significance for PF and MCV was probably due to the small number of children with complex FSs (Table5).

Table 3. Mean levels of HB, MCV, MCH, and PF among cases with FS and controls

Blood indices	Cases (100)		Controls (100)		p Value
	Mean	SD	Mean	SD	
HB g/L	106.5	13.3	108.6	10.2	0.27
MCV fl	73.3	5.1	74.0	4.9	0.36
MCH pg	25.1	3.6	25.7	3.1	0.26
PF µg/L	29.5	21.3	53.3	37.6	0.0001

HB, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PF, plasma ferritin; FS, febrile seizure.

Table 4. The number of children with low levels of HB, MCV, MCH, and PF among cases with FS and controls

Blood indices	Cases (100)	Percentage	Controls (100)	Percentage	P Value
HB g/L <110	35	35%	27	27%	0.38
MCV fl < 72	32	32%	24	24%	0.36
MCH pg < 24	33	33%	24	24%	0.28
PF µg/L < 30	65	65%	32	32%	0.000

Abbreviations as in Table 3.

Table 5. Mean level of HB, MCV, MCH, and PF among cases with complex and simple febrile seizures

Blood indices	Complex FS (12)		Simple FS (88)		p Value
	Mean	SD	Mean	SD	
HB g/L	97.2	14.4	107.9	12.6	0.016
MCV fl	70.7	5.1	73.6	5.0	0.09
MCH pg	22.9	4.0	25.5	3.4	0.03
PF µg/L	22.2	13.4	30.7	22.1	0.24

Abbreviation as in Table 3.

Discussion

Febrile seizures occurred more in males than females with a ratio of 1.5:1, which is similar to that of Wallace [16]. Increasing peak temperature has been reported to increase the risk of FSs progressively [3], but our data showed no marked differences in mean peak temperature at admission between cases and

controls. A similar increase in the risk of FSs has been reported in children with gastroenteritis as an underlying illness [10], but as shown in Table 2, the number of children with gastroenteritis was similar in both study groups. Family history of FSs, which most likely represents a genetic susceptibility to seizures with fever [3], and family history of epilepsy were higher among cases than controls in this study, but the differences were not statistically significant.

There is a controversy regarding the role of "iron status" in FSs. Pisacane [4] reported a significantly higher rate of iron-deficiency anemia among children with FSs than in controls, whereas Kobrinsky [5] suggested that anemia raises the threshold for FSs. In this comparative study, significantly lower PF levels were observed in the FS group than in the reference group. Other measures of iron status also were lower among FS patients, but the differences did not reach statistical significance. Our findings suggest that mild reduction in PF level ($\leq$ 30 µg/L) is associated with FS. Selection of this cut-off point for PF was arbitrary, because the commonly used cut-off point for iron-deficiency anemia is between 10 and 20 µg/L. However, few patients had levels of PF < 20 µg/L, and therefore I selected a higher cut-off point of 30 µg/L.

The lack of significant differences in HB, MCV, and MCH between the two study groups may be explained by the small sample size. Pisacane [4] studied the level of HB, MCV, and serum iron and found that in children younger than 2 years, 30% of FS children had anemia compared with 14% in the controls, but PF level was not measured in this study. Low level of PF may lower the seizure threshold, as iron is important for the function of various enzymes and neurotransmitters present in he central nervous system [11]. Fever may worsen the negative effects of low PF level on the brain, and therefore seizures can be triggered [4]. Of all indices of iron status measured in our study, PF was the only one that was significantly lower in FS patients compared with controls. Ferritin is an iron- containing protein that functions in the body as an iron-storage compound. Plasma ferritin provides a sensitive, specific, and reliable measurement for determining iron deficiency at an early stage, and it may be the best indicator of total body iron status [12]. It is known that ferritin is an acute-phase reactant that increases nonspecifically in response to any febrile illness [5]. Fever, however, was present in all patients in the two groups. Therefore differences in ferritin concentration between the two groups cannot be explained by fever. It was not possible to control other potential confounders such as maternal anemia, mother's tobacco use, and child's developmental delay because of lack of information on these variables in the present study. However, given the sociocultural background of the hospital referral population, it is likely that cases and controls will be homogeneous regarding these variables. Differences in HB, MCV, and MCH reflect differences in chronic iron status and are not affected by acute stress reactions. Iron deficiency and convulsions may be seen in children with lead poisoning [13]. However, lead poisoning is very unlikely in our study population because preliminary data from a study of children admitted to the same hospitals show that elevation of lead levels was very rare.

Selection bias as an explanation for the differences in iron status between the two groups is unlikely. Eligible children with and without febrile seizures were matched on age and sex. Both groups belong to the same socioeconomic status, as the two hospitals are state hospitals that attract average or below-average socioeconomic class patients. Although family history of FSs and epilepsy was higher in cases than in controls, these differences were not statistical significant. Cases and controls also did not differ in other possible risk factors for FS, as shown in Table2.

The exact explanation for the significant differences in the level of PF among children with FS compared with the reference group is unknown. Previous studies have reported a relation between iron-deficiency anemia and convulsions in patients with malaria [14]. Others reported that iron-deficiency anemia can cause developmental delay and behavioral disturbances early in life and early correction of anemia may reverse this [15]. The role of iron therapy in FS, however, should await further studies.

*In conclusion, febrile seizures are more common in males than females. There is significant association between iron deficiency anemia and febrile seizures (66%) versus (32%) in controls. Iron deficiency anemia may reduce the seizure threshold in the infancy and childhood. Low PF level is associated with and may play a role in FS.

*In recommendation, the role of iron therapy in FS, however, should await further studies. Other measures of iron status seem to be related to FS, but a large study may be needed to confirm this finding.

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Dept. of pediatric, Collage of Medicine, University of AL-Mustansirya