THE ASSOCIATION BETWEEN IRON DEFICIENCY ANEMIA AND FIRST FEBRILE SEIZURE: A CASE-CONTROL STUDY

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ABSTRACT

Background Febrile seizures (FS) are the most common type of seizures in children. The relationship between iron deficiency anemia (IDA) and first FS has been examined in several studies with conflicting results.
Purpose The purpose of this study was to determine the association between IDA and first FS.
Patients and Methods In this prospective case-control study we assessed 112 children with a diagnosis of first FS, aged between 5 months and 4 years who were admitted to the emergency unit of Hevi Children's Hospital in Duhok/Kurdistan region/Iraq, or who visited private office of the authors, during January 2006 to July 2009. The control group consisted of 120 febrile children without convulsion; controls were matched to the cases by gender and age. Patients and controls were reviewed to determine iron status using the hemoglobin concentration (Hb), mean corpuscular volume, S. iron, and total iron binding capacity.
Results A total of 35 (31.2%) of cases had IDA, compared to 14 (11.6%) of controls, which is statistically significant, P = 0.003.
Conclusion IDA was more frequent among children with FS than those with febrile illness alone. The results suggest that IDA may be a risk factor for FS and screening for IDA should be considered in children presenting with the first FS.

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Key words: Febrile convulsion, Iron deficiency, Anemia

Febrile convulsions (FCs), also referred to as febrile seizures (FSs), are the single most common type of seizure in children, affecting 2% to 4% of youngsters before their fifth birthday. It is defined as a seizure in a healthy infant or young child, between 3 months and 5 years of age that is associated with febrile, usually viral, illness (rectal temperature >38° C), but not with intracranial infection or dehydration or a history of nonfebrile seizures.[1] Most FSs occur between 6 months and 36 months of age, peaking at 18 months.[2] The occurrence of a child's first (initial) FSs has been associated with: first or second-degree relative with history of febrile and afebrile seizures,[3] day care attendance,[4,5] developmental delay,[3] Influenza A viral infection,[6,7] human herpesvirus-6 infection,[8,9] and iron deficiency anemia.[10]

There is a controversy regarding the role of iron status in FSs.

The aim of this case-control study was to evaluate the relation of IDA with first FS.

PATIENTS AND METHODS

Children with first FC who were admitted to the emergency unit of Hevi Children's Hospital in Duhok/Kurdistan region/Iraq, or who visited private office of the authors, between January 2006 and July 2009 were included. Children with prior afebrile seizure history were not included. The diagnosis of FC was made clinically by a pediatrician based on the history given by the mothers and observation of

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the fit and exclusion of CNS infection by normal CSF examination (lumber puncture was done only for children < 18 mo of age).

At the same time children of the same age group with acute febrile illness without convulsion were used as control group.

Age, sex, developmental milestones, family history of febrile seizures or epilepsy, mean of the temperature peak at admission, and the underlying illness were recorded for all cases and controls. The best up to date method for diagnosing IDA is the serum level of transferrin receptors, however, this technology is not within our reach, therefore patients and control group were evaluated to determine iron status using the Hb, mean corpuscular volume (MCV), S. iron, and total iron binding capacity (TIBC). Iron deficiency anemia was defined as the presence of hemoglobin concentration < 10.5 gm/dl, MCV < 70 fl, serum iron concentration of < 22 µg/dl, and TIBC > 400 µg/dl.[11]

The ethics committee at college of Medicine / University of Duhok approved the study. Chi square was used for statistical evaluation.

RESULTS

The study group consisted of 67 (59.8%) boys and 45 (40.2%) girls; a total of 112 children. The control group consisted of 70 (58.3%) boys and 50 (41.7%) girls; a total of 120 children.

The age groups and the number of patients and controls with IDA are shown in table 1. There was a significantly higher rate of IDA among children with febrile convulsions than in controls (31.2% vs. 11.6%), p = 0.003.

The hematological indices of patients and controls with IDA are shown in table 2. The development, family history of FC or epilepsy, the cause of fever and the mean of temperature peak on admission in patients and controls are shown in table 3.The differences were not statistically significant

DISCUSSION

The association between IDA and impaired neurocognitive function is well established, and this association holds even when potential confounders such as psychosocial and environmental factors are taken into account,[12] whereas, the association between IDA and febrile seizures has been described in the last decade with contradictory results. Infants and toddlers, who are undergoing critical neurocognitive development, may be at particular risk for such effects.[12]

In this study, IDA was more prevalent among the cases with febrile convulsion, as compared to the controls (31.2% vs. 11.6%); these findings are in accord with those of previous studies. Daoud et al[13] observed a significantly lower plasma ferritin in the first febrile convulsion group than in the reference group (49 of 75 vs.

Table 1. Age groups and number of anemic patients and controls

Age groups (mo)	Patients No. (%)	Patients with IDA	Controls No. (%)	Controls with IDA
< 6	2 (1.8)	0	2 (1.7)	0
7-12	14 (12.5)	3	17 (14.2)	1
13-18	39 (34.8)	14	43 (35.8)	6
19-24	32 (28.6)	10	34 (28.3)	4
25-32	9 (8)	2	11 (9.2)	1
33-36	6 (5.3)	2	8 (6.7)	0
37-48	10 (8.9)	4	5 (4.2)	2
Total	112 (100)	35 (31.2%)*	120 (100)	14 (11.6%)*

**p = 0.003*

Table 2. The hematological indices of anemic patients and controls (ranges)

	Patients with IDA (n=35)	Controls with IDA (n=14)
Hb (g/dl)	8.2-9.6	8.8-9.4
MCV (fl)	55-63	61-66
S. iron (µg/dl)	8-14	11-17
TIBC (µg/dl)	438-575	430-544

Table 3. The development, family history of FC or epilepsy, cause of fever, and tempt. peak on admission in patients and controls

	Patients No. (%)	Controls No. (%)	P value
Delayed motor development	7(6.3)	13 (10.8)	0.25*
•Delayed expressive speech	5(4.5)	3(2.5)	0.42*
•Family history of FC	13(11.6)	7(5.8)	0.15*
•Family history of epilepsy	8 (7.1)	7(5.8)	0.7*
•Cause of fever			
-URTI	62 (55.3)	89 (79.5)	0.16*
-LRTI	11 (9.8)	7 (5.8)	0.33*
-GE	14 (12.5)	10 (8.3)	0.34*
-Other viral infections	25 (22.3)	14 (11.7)	0.06*
•Mean tempt. on admission	38.8 ±5 ºC	38.8 ±8 ºC	

** Not significant*

24 of 75), and Dawn et al[14] and Pisacane[15] reported a significantly higher rate of IDA among children with febrile convulsions than in controls (15% vs. 9% and 30% vs. 12%, respectively), whereas, in contrast, Kobrinsky[16] reported that iron deficiency raises the threshold for seizures. Unfortunately, there are no national data on the prevalence of IDA among children in Iraq or in Duhok. Two large scale studies, the Third National Health and Nutrition Examination Survey (NHANES III) and the third report on nutrition monitoring in the United States, reported the prevalence of IDA in 1-2 year olds to be 3 % and in one to three year olds to be 15 %.[17] A more recent study, conducted in an urban setting with an equal mix of lower and middle socioeconomic groups, noted that 10 % of one to three year olds had IDA.[18]

The mechanism by which iron deficiency impairs neurologic function is unknown. Iron deficiency could impair neurotransmitter mechanisms, and it has been shown to decrease expression of dopamine receptors in the rat brain.[19] It may also interfere with myelination and alters myelin proteins and lipids in oligodendrocytes.[20] In addition, several enzymes in neural tissue require iron for normal function,[21] and monoamine and aldehyde oxidase are reduced in IDA,[22] which is common during the second and the third year of life and has been associated with behavioral and development disturbances.[23] Fever can worsen the negative effects of iron deficiency on the brain and a seizure can occur as a consequence.[15]

Although the family history of FSs and family history of epilepsy were higher

among cases than controls, the differences were not statistically significant. FCs are sometimes associated with inheritance of the so-called FC trait, a tendency to convulse with fever because of a low seizure threshold. Most studies suggest a dominant mode of inheritance with reduced penetrance and variable expression and increased frequency of FCs when a first degree relative has FCs.[24] In a child with FC trait, the risk of an FC is 10% for the sibling and almost 50% for the sibling if a parent has FCs as well.[24] Cases and controls also did not differ in other risk factors for FS (e.g. delayed development), as shown in table 3.

Lead toxicity, which interferes with the use of iron, is associated with low serum iron concentrations, lowers the seizure threshold, and could easily account for the apparent association between iron deficiency and seizures in these children.[15] However, lead poisoning is very unlikely in our patients and no data are available from the clinical records that might indicate whether lead poisoning was present in our patients, and children with febrile seizures are usually children who are well before and after fit, and afebrile convulsions are uncommon among them.

In conclusion, IDA may be a risk factor for the first febrile convulsion and a full blood count and screening for IDA will therefore be warranted in the work up of children with the first febrile convulsion.

However, further larger studies are required and other measures of iron sufficiency including plasma ferritin should be measured to confirm the findings in this study.

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پوختە

پەیوەندی دناڤ بەرا کەم خوینی یا کێم بوونا ئاسنی و ئێکەمین لەرزینا تایێ

بنەکوك: لەرزینا تایێ ژ مشەترین جورێن لەرزینا یە(فیی) ل نك زاروکا, گەلەك ڤەکولین بو شروڤەکرنا پەویەندیێ د ناڤ بەرا کەم خوینی یا کێم بوونا ئاسنی و ئێکەمین لەرزینا تایێ هاتینە کرن ب ئەنجامێن هەڤ دژ.

ئامانج: ئامنج ژ ڤێ ئەوە بو دیارکرنا پە وەندی دناڤ بەرا کەم خوینی یا کێم بوونا ئاسنی و ئێکەمین لەرزینا تایێ.

شێواز: رێژا خوینێ , تێکرایا قەبارێ خروکیچن سور , و رێژا ئاسنی دناڤ خوینێدا هاتە پیڤان بو 112 نەخوشێن تووش بوی ب ئێکەمین لەرزینا تایێ ئەوێن ژییّن وان دناڤ بەرا 5 مەها تا 4 سالان دماوێ ژ کانینا دووێ 2006 تا تیرمەهێ 2009 ,ل هەمان کات دە ئەو پیڤەر هاتنە کرن بو 120 زاروکێن تووشی تایێ بووین بێ لەرزین وەك گروپێ کونترول.

ئەنجام: کەم خوینی یا کێم بوونا ئاسنی هاتە دوست نیشانکرن ل نك 35 نەخوشا بەراوەدکرن دگەل 14 زارروکا ژ گروپێ کونترول.

دەرئەنجام و شیرەت: کەم خوینی یا کێم بوونا ئاسنی پتر یا بەربەلاڤە ل نك زاروکێن تووش بوی ب ئێکەمین لەرزینا تایێ.

الخلاصة

العلاقة بين فقر الدم الناتج عن نقص الحديد والاختلاجات الحرارية

الخلفية: الاختلاجات الحرارية هي من اكثر انواع الصرع شيوعا لدى الاطفال. اجريت عدد من البحوث لتفسير العلاقة بين فقر الدم الناتج عن نقص الحديد والاختلاجات الحرارية الاولى مع نتائج متناقضة.

الاهداف: الغرض من هذا البحث هو لمعرفة العلاقة بين فقر الدم والاختلاجات الحرارية الاولى.

الطرق: تم قياس نسبة الهيموكلوبين وحجم الكريات الحمرو نسبة الحديد في الدم ل(112) مريض مصاب باختلاج حراري اول،ممن تراوحت اعمارهم بين خمسة اشهر واربع سنوات للفترة من كانون الثاني 2006 ولغاية تموز2009 . وفي نفس الوقت تمت دراسة 120 طفلا مصابا بحمى بدون اختلاجات كمجموعة سيطرة.

النتائج: ظهر فقر الدم الناتج عن نقص الحديد في 35 مريضا مقارنة ب 14 طفلا من مجموعة السيطرة.

الاستنتاج والارشادات: فقر الدم الناتج عن نقص الحديد اكثر شيوعا بين الاطفال المصابين بالاختلاجات الحرارية , لذلك يجب التحري عن ذلك.