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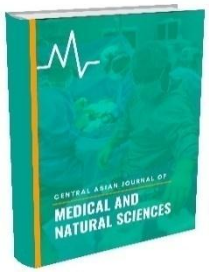

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THE RELATIONSHIP BETWEEN IRON DEFICIENCY AND FEBRILE SEIZURE IN A GROUP OF CHILDREN IN AL-ZAHRAA TEACHING HOSPITAL IN AL-NAJAF GOVERNORATE

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Abstract: Background: Febrile convulsions are prevalent in children aged between 6 months and 5years, with an incidence of 2-5%. On the other hand, iron deficiency is the most common hematologic disease of infancy and childhood with a periodof incidence that coincides with the time of developing febrile convulsions. Aim of study: To evaluate any association between iron deficiency& febrile seizures. Materials &Methods: Tow groups (n=60 in each) of 6-month to 5-year old febrile children, who were admitted to AL-Zahraa teaching Hospital in AL-Najaf AL-Ashraf city between 1st of February 2011 to 31th of December 2011. The first group, or the (FS group), included children with febrile seizure where the second group or the (control group), included febrile children without seizure. Blood samples were aspirated for measuring complete blood count (CBC) indices, serum Iron and total iron binding capacity (TIBC) levels. Results: Both groups were comparable for age, sex, &family history of febrile seizure. A total of 22 patient (36.6%) of cases had iron deficiency (Id), compared to 9 patient (15%)of controls respectively with p value=0.015. The blood indices in the FS group were lower than the control group and statstically, has significant difference in MCV, RDW, serum Iron level (p

value=0.042,0.032,0.015 respectively) between two groups while no significant difference was seen in TIBC, Hb%. also there was no significant difference regarding other variable like family history, duration of breast feeding. Conclusion. It was more frequent among children with FS than those with febrile illness alone. The results suggest that Id may be a risk factor for FS and screening for Id should be considered in children presenting with the first FS. The findings of this study suggested a positive association between iron deficiency and the febrile seizure in children.

Key words: breast feeding, iron level, FS group, Al-Zahra teaching, CBC level, TIBC level, MCV.

Introduction

Iron deficiency is a common disorder in pediatric patients. Although the most common manifestation is that of anemia, iron deficiency is frequently the source of a most of neurological disorders presenting to general pediatric neurologic practices. These disorders include developmental delay, stroke, breath-holding episodes, seizures, pseudotumor cerebri, and cranial nerve palsies . Although frequent, the identification of iron deficiency as part of the differential diagnosis in these disorders is uncommon and frequently goes untreated (1).

Febrile seizures are the commonest cause of seizures in children, occuring in 2-5% of children & are agonizing to the parent and child and can cause psychological trauma to both (2).

Iron deficiency is the commonest micronutrient deficiency worldwide, is a preventable and treatable condition (3).

Iron is needed for brain energy metabolism, for metabolism of neurotransmitters and for myelination. Thus, iron deficiency may alter the seizure threshold of a child (4,5).

Iron deficiency is postulated as a risk factor for febrile seizures in children and it is an easily correctable condition (6).

Its association with febrile seizures was first observed and published in mi d 90's in an Italian study (7).

Definition of Febrile seizures

FS are seizures that occur between the age of 6 months and 60 months with a temperature of 38^{O}C 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 a febrile seizures, Febrile seizures are the most common cause of convulsions in children and a frequent cause of emergency hospital admissions (2).

According to The National Institutes of Health (NIH) definition of a FS is "an event in infancy or childhood usually occurring between 3 months and 5 years of age associated with a fever, but without evidence of intracranial infection or defined cause for their seizure", after having excluded children with previous a febrile seizures (8).

In working practice, the lower age limit for FS is generally taken to be 6 months, given concerns regarding the possibility of an underlying serious but treatable infection in younger infants masquerading as a febrile seizure (e.g., meningitis). A simple FS is a generalized seizure, often tonic-clonic, lasting <15 minutes in duration, which does not occur more than once in 24 hours, and is followed by full recovery within 1 hour. Treatment for the actual seizure is generally not indicated, given the short duration. In >80% of children the duration of the febrile seizure is <10 minutes, and in only about 9% of children do they last >15 minutes (9).

Often, by the time the child presents to hospital, the seizure has already stopped. A FS may also be the presenting sign of a fever episode,while complex FS, which are characterised by any of the following features: >15 minutes in duration, focal symptoms, recurrence within 24 hours, and not followed by full consciousness within 1 hour. Investigations including neuroimaging and lumbar puncture are often warranted. Addressing parental anxiety forms a key part of the management of simple FS, because parents' (unspoken) worry with a first seizure is that their child might have died(9,10).

Incidence and prevalence of febrile seizure

About 2% to 5% of children in the USA and Western Europe, and 6% to 9% of infants and children in Japan will have experienced at least one febrile seizure, simple or complex, by the age of 5 years. Elsewhere the incidence varies, being 5% to 10% in India, and as high as 14% in Guam(11).

Patients and Methods:

Patients. A case –control study had been carried out at AL-Zahraa teaching hospital in Al-Najaf AL-Ashraf city the emergency unit and pediatric wards ,They had been admitted between Feb. 1 , 2011 to Dec. 31, 2011.

Sixty patients admitted with FS, their ages ranged from 6 months to 5 years.

They had temperature of 38°C or more without history of previous seizure attacks.

Control group: Control group included 60 children (6 months - 5 years of age) , had visited AL-Zahraa teaching hospital during same period of the study, They had a temperature of 38°C or more without history of previous seizure attacks.

They attended outpatient clinic for URTI, gastroenteritis, UTI or nonspecific causes of fever.

Data collection:

A special questionnaire (appendix 1) had been designed to collect data about the following :

Patients:

Information regarding the history:

- Name,sex,age,residence,date of admission,date of discharge,number of fits,type of fit ,duration of fit,duration of fever,rigor, sweating,fit onset after fever,associated symptoms,family history(in the first &second degree relatives) of febrile convulsion ,epilepsy ,developmental delayand feeding history.

Information regarding the examination:

- All patients were examined generally (level of consciousness ,pallor ,cyanosis. Jaundice ,lymphoadenopathy and organomegally)
- Vital signs(temperature, HR,RR)
- systematic examination & neurological examination

Investigation:

Following oral parents' consent, 2 blood samples (5cc) were taken :

- one with EDTA for evaluating CBC (Complete Blood Count).
- one clotted blood for evaluating Serum Iron &TIBC.

Classification of cases:

According to the type of fit:

- The cases of febrile convulsion were divided into 2 types(simple, complex) .A case was considered as a complex if one or more of the following criteria were present :
  (1) Seizure duration is >15 min.
  (2) Repeated seizures occur within 24 hr.
  (3) Focal seizure activity or focal findings are present .
- Blood indices(Hb% ,MCV,RDW,S,IRON,TIBC) was studied in relation to age ,sex ,family history of FS, The type of FS, feeding history.

Control group

Information related to the control group were collected included:

Name,sex,age,residence,family history(in the first &second degree relatives) of febrile convulsion,epilepsy and developmental delay

Then following oral parents' consent, 2 blood samples (5cc) were taken

- one with EDTA for evaluating CBC (Complete Blood Count).
- one clotted blood for evaluating Serum Iron &TIBC.

Diagnosis of Iron Deficiency The diagnosis of Id in children is challenging. A low mean cell volume (MCV) reflects microcytosis that is seen with Id. The red cell distribution width (RDW) reflects anisocytosis, the variance of cell size that increases with Id(3,22).

Therefore, the iron status of patients was determined using the definition of Id as a MCV < 72 fL , RDW >15% , S.iron <22mg/dl &TIBC>400mg/dl.

Anemia was diagnosed when the hemoglobin was <10.5 g/L, We choose the values for MCV of <72 fL and hemoglobin of <10.5 g/L as our diagnostic threshold as these are acceptable age appropriate values(50). As RDW varies per laboratory, it is recommended to use the cutoff value identified by the local laboratory, with the lowest acceptable value being 13%. We therefore chose 15% as the upper limit of normal for RDW, the cutoff value used by our laboratory.

Exclusion criteri as:

- Past history of any a febrile seizure .
- Past history of hereditory blood disorder like heamoglobinopathy
- History of neurodevelopmental delay .

- Age below 6 months & above 5 years .
- Cases of CNS infection: They were excluded depending on clinical features(lethargy, irritability, vomiting, nuchal rigidity, bulging fontanel, headache, drowsiness, toxicity and coma). And /or positive laboratory tests.

Results

A total of 75 potential cases and 79 potential controls were reviewed to obtain the cohort of 60 cases and 60 controls (final control-to-case ratio 1:1).

Reasons for exclusion of 15 cases included the following:

(a)exclusion criteria met (7)

(b)missing data (2)

(c)second presentation resulting in duplication of patient (4)

(d)lab work not done (2)

Reasons for exclusion of 19 controls included the following:

(a) exclusion criteria met (15)

(b) missing data (2)

(c) second presentation resulting in duplication of patient (1)

(d) lab work not done (1)

According to parameters which mention previously about diagnosis of ID (MCV<72fl, RDW>15%, serum iron <22mg/dl, TIBC>400mg/dl) we found 22 ,9 cases had ID in febrile convulsion & control respectively as shown in table 3.1

Table 3.1 shows significant differences between cases and control regarding number of patient had ID.

TABLE3.1 comparison between case & control whether they had ID or no ID.

	Cases n=60	Percentage (%)	Control n=60	Percentage (%)
ID	22	36.6%	9	15%
No ID	38	63.4%	51	85%
TOTAL	60	100%	60	100%

We found there's no significant difference regarding peak temperature on admission, age ,sex and low social class ,also we found number of patient had iron deficiency in febrile seizure group

more than those in control group and there's significant differences between two group as shown in table 3.2.

TABLE 3.2 The differences in demographic characteristics, peak temperature on admission, and Laboratory Values among cases of FS and controls.

Variable	*Patients*	control	P value
Temperature peak on admission in °C: mean	38.9	38.4	0.364
Age(months): mean	18.25	17.9	0.449
Gender male %	42(70%)	38(63.3 %)	0.323
Low socioeconomic level	33(55%)	28(46.6)	0.124
Family history of febrile seizure	15(25%)	8(13.3%)	0.081
Hb%(g/L) mean	10.9	12.1	0.236
MCV(fl) mean	72.64	76.53	0.032*
RDW % mean	15.94	13.305	0.042*
Iron deficiency	22(36.6 %)	9(15%)	0.025*

From the total of 60 cases of febrile seizures we found 16 patients had complex seizures & 44 patients had simple febrile seizures .

Statistically there is significant differences between complex and simple seizures regarding MCV (0.026), RDW (0.044), but there is no significant differences regarding S.iron (0.387) ,TIBC(0.228) as shown in table 3.3

TABLE3.3 Mean level of Hb%, MCV, RDW S.iron&TIBC among cases with complex and simple febrile seizures

Blood indices	Complex FC	Simple FC	P value

	Mean	Mean	
Hb%	**11.8**	**11.2**	**0.343**
MCV	**72.53**	**74.34**	**0.026***
RDW	**14.5**	**16.4**	**0.044***
S. iron	**74.57**	**68.75**	**0.387**
TIBC	**285.00**	**304.18**	**0.228**

Family history of febrile convulsion, were studied in both cases and control and presented in Table (3.6).This table shows that family history of febrile convulsion was positive in 15 (25%) of cases, while in control the family history of febrile convulsion was positive in 8 (13.3%), the difference was statistically not significant as shown in table 3.4.

TABLE 3.4 Mean level of Hb, MCV, RDW, S.Iron&TIBC among cases and control regarding positive family history.

Blood indices	Cases F.H + N=15	Control F.H+ N=8	P value
	Mean	Mean	
Hb%	**11.16**	**12.23**	**0.785**
MCV	**73.60**	**78.35**	**0.432**
RDW	**14.21**	**14.60**	**0.126**
S. iron	**66.89**	**77.69**	**0.715**
TIBC	**301.3**	**297.2**	**0.401**

We found the blood indices in patient with feeding history less than 6 months lower than those more than 6 months but statistically there's no significant difference between them as shown in table 3.5.

TABLE 3.5 Mean level of Hb, MCV, RDW, S.Iron&TIBC among cases regarding duration of breast feeding whether less than 6months or more

Blood	Breast	Breast feeding	P value

indices	feeding > 6months	< 6months	
	mean	Mean	
Hb%	11.8	11.2	0.432
MCV	74.4	72.2	0.213
RDW	13.9	14.8	0.367
S. iron	84.5	75.3	0.256
TIBC	287.3	330.6	0.211

Blood indices found in patient from urban area lower than patient from rural area but Statistically we found there's no significant differences between them as shown in table 3.6.

TABLE 3.6 Mean level of Hb, MCV, RDW, S.Iron&TIBC between cases &control regarding residency whether urban or rural area

Blood indices	CASE		CONTROL		P value
	URBAN	RURAL	URBAN	RURAL	
Hb%	12.3	13.5	11.3	11.8	.169
MCV	74.06	78.46	75.25	78.77	.051
RDW	14.8	13.9	13.6	12.7	.210
S. iron	66.8	74.5	83.0	93.3	.377
TIBC	297.2	301.3	260.8	218.9	.560

Discussion

Iron is an essential element in the metabolism and functioning of enzymes required in neurochemical reactions. These include monoamine oxidase, cytochrome, peroxidase and catalase, the mechanism by which iron deficiency impairs neurologic function is unknown (7,13).

Fever can worsen the negative effects of iron deficiency on the brain and a seizure can occur as a consequence (7)

we did comparison between case & control whether they had Id or no Id in table 3.1 we found significant differences between cases and control regarding number of patient had Id by measuring blood indices and serum iron level this result similar as Vaswani et al. in india(16) ,this result may be explained by several enzymes in neural tissue require iron for normal function, (14) and monoamine and aldehyde oxidase are reduced in IDA, which is common during the second and the third year of life and has been associated with behavioral and development disturbances(15).

Regarding comparison of multiple blood Indices (Hb%, MCV, RDW, S.IRON,TIBC) between cases &control in table (3.2) the result of(Hb%, MCV, S.IRON) lower in the cases than control group but there was significant difference seen in the serum iron level , RDW & MCV (Pvalue= 0.015,0.042&0.032 respectively) .

Similar results were observed by Hartfield et al (17) conducted a retrospective case control study in Canada and determined iron status using MCV, RDW, and hemoglobin.

To explore if those with complex febrile seizures were more likely to have Id we examined the association between seizure type (complex versus simple febrile seizure) and hemoglobin, MCV, and RDW. In table 3.3 The mean hemoglobin of the 16 patients with complex seizures was 11.8 g/L compared with 11.2g/L in the 44 patients with simple febrile seizures (P.343). this difference is statistically not significant,&both values are within the normal range of hemoglobin for age and are not clinically important.& also there's significant difference regarding MCV, RDW . There was no significant difference found with S.IRON ,TIBC between those having complex and simple febrile seizures ,this result similar to Batieha et al. (18), study in Jordan ,also Similar results were observed by Rehman et al. (19)

Family history of FSs, table 3.4 which most likely represents a genetic susceptibility to seizures with fever and family history of FS were higher among cases than controls in this study, but the differences were not statistically significant. this result similar to study Batieha et al. (18) in Jordan while in another study in Iran (20) show there's significant differences regarding family history of FSs.

Also we found the duration of breast feeding between cases and control were important, where those had breast feeding less than 6 months more vulnerable to febrile seizure than those had breast feeding more than 6 months but statistically no significant differences but our result are incompatible to study done in Iran(20), which show there's significant differences regarding duration of breast feeding.

Mature human milk and cow milk contain the same amount of iron, approximately 0.5 mg/L; fortified formulas contain 10 to 13 mg/L. However, about 50% of iron from human milk is absorbed compared with only10% from cow milk and less than 5% from iron-fortified formula. The reasons for the enhanced bioavailability of iron from human milk are not well understood, but they include a lower concentration of calcium and a higher concentration of ascorbic acid in human milk (21,22).

Other characteristic features of the patients and their control were studied,regarding the residence table 3.5 , Statistically there is no significant differences in the blood indices between case and control regarding urban or rural area but blood indices in urban area lower than from rural area .

In our study, iron deficiency was diagnosed by four criteria i.e. MCV, red cell distribution width (RDW), serum iron &TIBC and three parameters of them (MCV, RDW, serum iron) Statistically show significant difference among patients and controls.

In the study done by Pisacane, et al. (7). among children of the same age group, similar results were noted, iron status was measured by hemoglobin, MCV and serum iron in that study.

In Dawn, et al. (17). Iron status was measured by RDW, MCV also found similar results with children with febrile seizures almost twice likely to have iron deficiency compared to controls.

In the study by Daoud, et al. (18) the significance of iron status as a possible risk factor was evaluated.

Similar observations were made in a study done by Vaswani, et al (16) from Mumbai.

In Leela kumari et al. (23) study in India iron deficiency was diagnosed by three criteria i.e. Hb%, red cell distribution width (RDW), serum ferritin, and he found all three parameters were significantly different among cases and controls.

The RDW is the first parameter to be affected in Id, even prior to changes in ferritin, serum iron levels, TIBC (total iron binding capacity), transferrin saturation, FEP (free erythrocyte protoporphyrin), cell size, and hemoglobin level. Several studies have found that the RDW alone or in combination with MCV is an effective screening tool for Id in children and often superior to other measures (16, 24, 25, 26).

Kim et al (24) found that the sensitivity of RDW was 83.3% and specificity was 57.7% in diagnosing IDA. For MCV, they found the sensitivity and specificity to be 99% and 53.8%, respectively,

A combination using both MCV and RDW resulted in a positive predictive value of 97.8% in the diagnosis of IDA.

Traditional measures of iron status (ferritin, serum iron, TIBC, transferrin saturation, and FEP) are influenced by infection and are therefore not reliable indicators of iron status in the setting of acute infection (27,28).

Conclusion

Our stuy, found that children with febrile seizureswere likely to be iron deficientwhen compared with controls. We would proposethat Id is one of the risk factors for febrile seizureto be included along with others such as family history,rate of rise of fever, and specific viral illness.The chance of a child having a febrile seizure mayincrease as the number of risk factors in a givenpatient accumulates.

Recommendations:

(1) Screening for Id with a thorough nutritional history and laboratory blood indices like RDW,MCV,It follows that therapy for those with Id may decrease the risk of seizurerecurrence and will prevent other squeals of Id in the young.

(2) Breast feeding should be encouraged as absorption of iron high reach to 50 % and breast fed infant beginwith iron supplements from 4 months until at least 12 months of age with 1mg/kg/day of elemental iron in the form of medicinal iron drops or syrup.

(3) Early detection and management ofiron deficiency inall health centers as being a risk factor of FS.This may be done byproviding the primary health centers with enough medications in order to apply early and proper treatmentof iron deficiency&other causes of fever.

(4) When breast feeding is not possible, only iron fortified formulas should recommended up to 12 months of age.

(5) Weaning food (cereal, milk formulas) should be iron fortified.

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