Association of febrile convulsion with serum sodium and hematological indices among Iraqi children in Diyala province

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Abstract

Background: Several studies had documented the relationship between iron deficiency and low serum sodium levels with the risk of developing recurrent seizure among children within the same febrile illness.

Objectives: To figure out the association between serum sodium levels and iron deficiency with occurrence of febrile convulsion in children between 6 months to 6 years old in Diyala province.

Patients and Methods: A case control study was conducted in Al-Batool Teaching Hospital for Maternity and Children, Diyala-Iraq during a period from September 2017 to March 2018. 200 patients aged between 6 months to 6 years were enrolled, 100 of them were diagnosed with febrile convulsion and the other 100 were age and sex matched apparently health children as controls. Patients aged < 6 months or > 6 years, cerebral palsy, meningitis, epilepsy, severe gastroenteritis and dehydration, history of chronic drug use, and history of developmental delay were excluded from this study. Diagnosis of febrile convulsion was based on initial evaluation focusing on the source of the fever and thorough physical examination for the presence of meningeal signs and the child's level of consciousness. All patients were subjected to detailed history, complete physical and neurological examination, laboratory investigations and lumbar puncture which proceeded by fundoscopy examination. Human privacy was respected by taken child's parents consent. Accumulated data were analyzed using the SPSS version 25. The independent t-test (two tailed) was used and P value less than 0.05 were considered significant.

Results: There was a significant lower means in patients regarding total red blood cells (4.61 *vs* 4.76, P= 0.032), hemoglobin concentration (11.38 *vs* 11.85, P= 0.003), packed cell volume (34.07 *vs* 37.67, P= 0.001), mean corpuscles volume (74.06 *vs* 78.01, P= 0.001), and higher red distribution width mean (14.73 *vs* 13.51, P= 0.001). Furthermore, a significantly lowered means in serum iron (mg/dl) (4.02 *vs* 4.74, P= 0.008), serum ferritin (ng/mL) (46 *vs* 58.58, P= 0.001), serum sodium (mEq/L) (131.11 *vs* 139.89, P= 0.001) and higher total iron binding capacity (μg/dL) (80.84 *vs* 66.12, P= 0.001) among patients compared to controls.

Conclusion: Children with febrile convulsion are more likely to have iron deficiency anemia and hyponatremia.

Keywords: Febrile convulsion, blood indices, serum sodium, Diyala.

Introduction:

Febrile convulsion (FC) is the single most common convulsion type. It considered benign, but there is a small subset of children that present with convulsion and fever may have recurrent FC or develop epilepsy [(1).] The American Academy of Pediatrics (AAP) defined FC as a convulsion occurring in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of a FC [(2).]

Clinicians classifying FC as either simple (generalized, lasting < 15 minutes, generalized tonic and clonic activity without a focal component and without recurrence within 24 hours or within the same febrile illness) or complex (focal onset, occurs more than once during a febrile illness, or one that lasts ≥ 10-15 minutes and recurrent FC within 24 hours of the first episode) [(3).] FC occur in 2% to 5% of children six months to five years of age, with the peak incidence occurs at 18 months of age and is low before six months or after three years of age, the incidence decreases markedly after four years of age and rarely occurs in older than seven years of age [(4).]

Males have a higher frequency of FC (male to female ratio, 1.1:1 to 2:1), also there are two seasonal peaks in FC incidence according to the peak of viral upper respiratory infection [(5).] Elevated brain temperature alters many neuronal functions, as many temperature-sensitive ion channels, which influences neuronal firing and increases the probability of generating massive neuronal activity [(1).]

Additionally, the fever-promoting pyrogen interleukin-1β synthesis in the hippocampus has been shown to increase neuronal excitability, acting via both glutamate and Gamma-Aminobutyric acid (GABA) [(6).] Provoking risk factors for FC include genetic factors, as there is a variable inheritance pattern, with no single accepted mechanism.

A positive family history of FC can be found in 25–40% of cases, significant higher rates are seen for FC in monozygotic twins as compared to dizygotic twins in multiple twins [(7).] Intrauterine risk factors also have a role as fetal growth retardation, low birth weight and short gestational age are significant risk factors for FC **(8).** Iron deficiency is a provoking factor for FC, since iron is important for neurological functioning as neurotransmitter metabolism, myelin formation, and brain energy metabolism [(9).]

When iron supply does not meet iron demand, the fetal brain may be at risk even if the infant is not anemic [(10).] Low serum iron and presence of anemia can serve as a reinforcing factor for the febrile seizure in children [(11).] Furthermore, there is a relationship between hyponatremia and risk of recurrent convulsion within

the same febrile illness, hyponatremia may play a role as a risk factor for recurrent FC. Patients with active seizures should be managed with airway management, high-flow oxygen, supportive care, and anticonvulsants as necessary such as rectal diazepam (0.5 mg/kg) and buccal 0.4-0.5 mg/kg) or intranasal (0.2 mg/kg) are effective and can be given at home for a seizure lasting longer than five minutes [(12).]

In regard to prognosis and outcome, four potential adverse outcomes of FC that theoretically may be altered by an effective therapeutic agent which include; decline in intelligence quotient (IQ) [(2)]**.** Increased risk of epilepsy (risk of epilepsy is increased 5.43-fold after febrile convulsions), Risk of recurrent convulsions, and finally death [(13–15)]

Patients and Methods:

A case control study was conducted in Al-Batool Teaching Hospital for Maternity and Children, Diyala-Iraq during a period from September 2017 to March 2018. It aims to figure out the association between serum sodium levels and iron deficiency with occurrence of febrile convulsion in children between 6 months to 6 years old in Diyala province The study population includes 200 children aged between 6 months to 6 years old. 100 patients admitted to the hospital with febrile convulsion (patient group) and the other 100 were age and sex matched apparently healthy children as control group who were collected from primary healthcare centers.

Patients aged less than 6 months and more than six years, known case of cerebral palsy, meningitis, epilepsy, those with severe gastroenteritis and dehydration, those with history of chronic drug use or developmental delay were excluded from this study. Diagnosis of febrile convulsion was based on initial evaluation focusing on the source of the fever and thorough physical examination for the presence of meningeal signs and the child's level of consciousness. All patients were subjected to detailed history, complete physical and neurological examination, laboratory investigations including; complete blood count, serum sodium (Na), Calcium (Ca), Phosphorus (Ph), potassium (K), Chloride (Cl), random blood sugar, and highly sensitive C-reactive protein (H-CRP). Additionally, lumbar puncture was to determine the cause of FC which proceeded by fundoscopy examination to exclude increased intracranial pressure.

A questionnaire form was specially designed for gathering the necessary information that was filled by the researcher. Human privacy was respected by taken child's parents consent. Accumulated data were analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the continuous variables among study groups. A level of P value less than 0.05 was considered significant.

Results:

The mean age of the patients was 27.75 ± 19.8 months. 51% of them were females. 99.5% of study patients were full term during delivery and 43% of them have no family history of febrile convulsion. the majority of study population in each group (91% of patients and 98% of controls) were vaccinated regularly as shown in table (1).

Table (1): Distribution of study subjects by general characteristics.

Variable		Patient (%) (n= 100)	Control (%) (n= 100)	P value
Age (Ms)	< 12	10 (10.0)	37 (37.0)	0.880
	12 - 35	57 (57.0)	31 (31.0)	
	≥ 36	33 (33.0)	32 (32.0)	
Gender	Male	49 (49.0)	60 (60.0)	0.118
	Female	51 (51.0)	40 (40.0)	
Vaccination History	Regular	91 (91.0)	98 (98.0)	0.030 [S]
	Irregular	8 (8.0)	2 (2.0)	
	Unvaccinated	1 (1.0)	0	
Previous hospitalization	Yes	55 (55.0)	0 (0)	**
	No	45 (45.0)	100 (100.0)	
Cause of previous admission (n= 45)				**
	Fever and Fit	27 (60.0)	0	
	Chest infection	8 (17.8)	0	
	Gastroenteritis	10 (22.2)	0	
Site of delivery	Hospital	88 (88.0)	63 (63.0)	0.0001 [S]
	Home	12 (12.0)	37 (37.0)	
Mode of delivery	NVD	42 (42.0)	16 (16.0)	0.0001 [S]
	C/S	58 (58.0)	84 (84.0)	

[S] Significant association at P < 0.05 levels.

Table (2) shows the distribution of patients by clinical features of fit. The most common type of fit was generalized (99%) and 95% of fits were lasted for less than 15 minutes and occurred almost at equal rates during day or night (51% *vs* 49%). On the other hand, the majorities of study patients have neither febrile convulsion attack during hospital stay (90%) nor developed fit previously (78%).It was noticed that tonsillitis represented the most common cause of fever (59%). In 82% of cases, fever presented for less than 12 hours and most of the patients were presented with a temperature ≥ 39 (82%).

All parameters including serum iron (mg/dl) (4.02 ± 2.38 *vs* 4.74 ± 1.31, P= 0.008), serum ferritin (ng/mL) (46 ± 24.61 *vs* 58.58 ± 15.28, P= 0.001), total iron binding capacity (µg/dL) (80.84 ± 14.51 *vs* 66.12 ± 11.96, P= 0.001), and serum sodium (mEq/L) (131.11 ± 3.27 *vs* 139.89 ± 8.38, P= 0.001) were significantly lowered in patients compared to controls as shown in table (3).

A comparison of mean ± SD of certain serum biochemical between study groups was shown in table (4). Parameters including serum iron (mg/dl) (4.02 ± 2.38 *vs* 4.74 ± 1.31, P= 0.008), serum ferritin (ng/mL) (46 ± 24.61 *vs* 58.58 ± 15.28, P= 0.001), and serum sodium (mEq/L) (131.11 ± 3.27 *vs* 139.89 ± 8.38, P= 0.001) were significantly decreases in patients compared to controls. On the contrary, the total iron binding capacity (µg/dL) (80.84 ± 14.51 *vs* 66.12 ± 11.96, P= 0.001) was significantly higher in patients compared to controls.

Table (2): Distribution of study patients by clinical features of fit and fever.

Variable		No. (n=100)	Percentage (%)
Type of fit	Generalized	99	99.0
	Focal	1	1.0
Duration of fit	< 15 mint	95	95.0
	≥ 15 mint	5	5.0
Time of Fit	Day	51	51.0
	Night	49	49.0
Another fit attack in hospital	Yes	10	10.0
	No	90	90.0
History of previous fit	Yes	22	22.0
	No	78	78.0
Cause of fever	Tonsillitis	59	59.0
	Chest infection	23	23.0
	Acute GE	16	16.0
	Otitis Media	2	2.0
Duration of fever (Hrs)	≤ 12	82	82.0
	> 12	18	18.0
Temperature on admission (^{0} C)	< 39	18	18.0
	≥ 39	82	82.0

Table (3): Comparison of hematological parameters among study groups.

Variable	Study groups		Student t-test	P Value
	patients Mean ± SD	Controls Mean ± SD		
Red blood corpuscles (millions / cu.mm)	4.61 ± 0.51	4.76 ± 0.43	**2.158**	**0.032**
Hemoglobin concentration (grams/deciliter)	11.38 ± 1.22	11.85 ± 0.9	**3.024**	**0.003**
Packed Cell Volume	34.07 ± 3.18	37.67 ± 5.7	**5.457**	**0.001**
Mean Corpuscles Volume	74.06 ± 8.19	78.01 ± 5.42	**3.997**	**0.001**
Mean Corpuscles Hemoglobin	25.58 ± 5.62	25.06 ± 2.35	**0.851**	**0.396**
Red Distribution Width	14.73 ± 1.85	13.51 ± 1.08	**5.626**	**0.001**

[S] Significant association at P < 0.05 levels.

Table (4): Comparison of certain biochemicals among study groups.

Variable	Study subjects		Student t-test	P value
	Patients Mean ± SD	Controls Mean ± SD		
Serum iron (mg/dl)	4.02 ± 2.38	4.74 ± 1.31	**2.65**	**0.008**
Serum Ferritin (ng/mL)	46.0 ± 24.61	58.58 ± 15.28	**4.343**	**0.001**
Serum TIBC (µg/dL)	80.84 ± 14.51	66.12 ± 11.96	**7.828**	**0.001**
Serum Sodium (mEq/L)	131.11 ± 3.27	139.89 ± 8.38	**9.761**	**0.001**

[S] Significant association at P < 0.05 levels.

Discussion:

Undoubtedly, besides it is the leading study in this medical field, at least in our province. The importance of this study may emerge from several trajectories; firstly, the subject of the study itself, the FC in infants, is well attested in our traditional culture since antiquity as one of the diseases that leaves a horrible impression among population, specially the mothers, due to its bad consequences. Secondly, in our community, there are wide ranges of common illnesses that under their unfavorable complications may lead to FC which usually have unfortunate outcomes. In this study, the means of red blood cells, Hemoglobin (HB), Packed cell volume (PCV), mean corpuscles volume (MCV) were significantly higher in healthy patients compared to patients with FC, while mean of red distribution width (RDW) was significantly lower (P< 0.05) and no significant difference in mean of mean corpuscles hemoglobin (MCH) between them (P= 0.396). Similar studies in Pakistan in 2005 **(16).** in Iran in 2014 **(17).** in India in 2010 **(18).** in Iran also in 2013 **(19)** and in Pakistan in 2013 **(20)** in which found, Hb, MCV and MCH results being similar to present study and concluding that low body iron plays an important role in brain metabolism, can down regulate halting many substantial functions of brain and could lead to FC. Differently, in Iranian study in 2009, the amount of Hb, MCV, MCH, and MCHC were non-significantly higher among cases than controls and Iron deficiency anemia was less frequent among the cases with FC **(21).** which was in agreement with an Iraqi one in 2008, as noticed that low HB, MCV and MCH, were non- significantly higher among cases than controls (P> 0.05) **(55).** The major causes behind different results may include the difference in the age and sample size and different diagnostic criteria of anemia.

This study showed that means of serum iron, and serum ferritin were significantly higher in healthy patients compared to patients with FC, while mean of total iron binding capacity was significantly lower (P< 0.05). These results are consistent with Iranian study conducted in 2012 **(17)** in Pakistan in 2005 **(18).** and in Jordan in 2005 **(23).** as researcher showed that serum ferritin were significantly lower in patients with FC than in patients with febrile illness without convulsions (P < 0.05), In contrast, absence of relationship was noticed between iron-deficiency anemia and first FC in Iranian study in 2003 **(24).** Iron-deficiency anemia was less frequent among patients with FC in Iran also in 2009 **(21).** these explained by the role of ferritin, as an acute-phase reactant that increases in response to any febrile illness and these differences observed might related to the difference in sample size and using different patient age groups.

Regarding the mean of serum sodium, it was significantly lower in patients complaining from FC compared to healthy patients (131.11 ± 3.27 versus 139.89 ± 8.38, P= 0.001), which was similar to an Iraqi study in 2017 **(25).** an American one in 2004 **(26).** and an Iranian study in 2016 **(27).** in which serum sodium in the case group was significantly lower than control (P < 0.05) and there is a relationship between hyponatremia and recurrent FC, i.e., hyponatremia play as risk factor for recurrent febrile convulsion. In contrary to the current results, Indian study in 2011 **(28).** and Iranian one in 2009 **(29).** found no significant difference in the mean serum sodium between the patients and controls in simple FC and the simple FC with recurrence groups. These differences in observations may be attributed to the sample size in each study, etiology of convulsion, since the fact that some control group consisted of children with afebrile seizures and not febrile children without convulsions, as was observed in some studies compared with it. Therefore, Children with febrile convulsion are more likely to have iron deficiency anemia and hyponatremia.

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