Iron profile parameters and serum zinc & copper levels in children with febrile convulsions in Banha

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Abstract: Background: Febrile convulsions is a common disorder in childhood. There are different hypotheses about neurotransmitters and trace element changes in biological fluids which can have a role in pathogenesis of febrile convulsions. **Objectives:** We aimed to investigate level of zinc, copper and iron profile parameters in 40 children with simple febrile convulsions aged between 6 months and 3 years and compare them with 40 age-matched controls with febrile illness without seizures in Banha city in Egypt. **Methods:** After informed consent, detailed history was taken and clinical examination was performed for both cases and controls, blood lab to measure serum ferritin by ELISA, iron, zinc and copper levels by Colometric method were performed for all studied children. **Results:** The median serum ferritin levels in cases and controls were 10 and 46.5 µg/dl, respectively, the difference was statistically highly significant **(*P* = 0.00)** and the median serum zinc levels in cases and controls were 53 and 95 µg/dl, this difference was statistically highly significant (***P* = 0.00**). Also the median serum copper level in cases and controls were 120 and 93 µg/dl, the difference was statistically not significant **(*P* >0.05).** We found positive correlations between occurance of febrile convulsions and positive family history of febrile convulsions, malnutrition. Low serum levels of hemoglobin, iron, ferritin and zinc. **Conclusion:** Serum ferritin and zinc deficiency are risk factors for simple febrile convulsions while serum copper show no significant changes in cases of febrile convulsions. **Recommendation:** Providing adequate iron and zinc supplementation in early childhood may lead to significant decreases in febrile convulsions incidence in young children.
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Key words: Febrile convulsion, Serum iron, zinc, copper, trace element.

1. Introduction:

FCs are defined as seizures in neurologically healthy infant/children between 6 months and 3 years of age with fever > 38.4 °C but without evidence of intracranial infection as a cause and no previous history of FC. Seizures with fever in children who have suffered a previous non-FC are excluded. This definition excludes seizures that accompany meningitis, electrolyte imbalance or toxic encephalopathy **(*Allen et al., 2007*).** Simple febrile seizures are generalized, tonic–clonic seizures lasting less than 15 minutes that do not recur within 24 hours or within the same febrile illness **(*Angle, 2006)***. Febrile seizure has multiple etiological factors. Of these, low serum zinc and iron levels in febrile seizures have drawn much attention. **(*Daoud et al., 2002*).**

Iron is needed for brain energy metabolism, for metabolism of neurotransmitter and for myelination, Iron deficiency was suggested to alter the seizure threshold in children**. (*Beard, et al., 2008).***

Trace elements have been shown to influence a number of biochemical and physiological processes, they are incorporated into the structure of proteins, enzymes, and complex carbohydrate **(*Vural, et al 2005).***

Zinc and copper are essential trace elements that have been studied in many diseases, they play a key role in brain function, development and prevention of neurlogical disorders. Also it has been hypothesized that other trace elements e.g. selenium may be implicated in the etiology of febrile convulsions ***(World Health Organization, 2007).***

This study was conducted to measure iron profile parameters, serum zn & cu levels in children with febrile convulsions and compare them with those of control subjects.

2. Subjects and methods:

This case-control study was conducted from December 2012 to June 2013 in Benha University and Benha Children Hospitals. The study included 40 infants/children, aged between 3 months and 6 years, who presented with simple febrile seizure. All these children had normal neurological examination. Samples were collected in emergency room. Forty children of the same age range visiting the outpatient department for fever served as the controls. Children with documented intracranial infection, and those on zinc or iron for therapeutic purposes were excluded. Subjects were subjected to thorough history taking (age - duration of fever- character of febrile convulsion), complete clinical examination (body measurements-

vital signs-CNS examinations) and blood investigations (CBC (by cell counter(sysmex-21kx), serum iron, TIBC (SPECTRUM – CAT.NO.270 001), zinc (GREINER - CAT.NO.184 000), copper (GREINER - CAT.NO.162 000) by (colometric methods) and serum ferritin (NOVATEC) by (ELISA) (intra assay variation <5.4%, inter assay variation <6.1%. Three ml of venous blood were collected from each child under aseptic conditions one ml was put on EDTA for performing C.B.C, the rest of the blood left in plain tube until clot. Then separation of serum by centrifugation and the resultant serum was stored in epindorf tube at -20°C till the time of assay.

Statistical analysis:

The collected data were coded, tabulated, and statistically analyzed using SPSS program and version 16. Inferential analyses were done for quantitative variables using independent T-test and Mann-whiteny test. Inferential analyses were done for qualitative data using Chi square test. Correlations were done using Pearson correlation.

3. Results:

40 cases and 40 controls were included in the study. The average age of cases and controls was 11 and 9.5 months, respectively. Also 35 cases (87.5%) were females and 5 cases (12.5%) were male with no significant difference between them **(*P* < 0.05)**. There was significant difference between cases and control regarding positive family history of febrile convulsion & malnutrition but no significant difference regarding other history data (Table 1). Also there was significant difference between cases and control regarding heart rate but no significant difference regarding temperature & respiratory rate (Table 2). There was significant difference between cases and control regarding haemoglobin level in g/dl and RDW% (Table 3). The median serum iron level in cases was 34 µg/dl, and in controls was129 µg/dl, this difference was statistically highly significant (***P* = 0.00)**. The median serum TIBC level in cases was significantly higher than controls (449&316 µg/dl) respectively, (***P* =0.00**) (Table 4). Median serum levels of ferritin was significantly lower in FC patients than control patients 10µg/dl vs 46.5 µg/dl with ***P* <0.01**). The median serum copper level in cases was higher than control (120 µg/dl vs 93 µg/dl ***P* > 0.05**). Serum zinc level in FC cases was significant lower than control 53µg/dl vs 95 µg/dl ***P* = 0.00)** (Table 4). There was significant positive correlation between occurrence of febrile convulsion and presence of positive family history of FC and malnutrition. There was significant negative correlations between occurrence of febrile convulsion and each of haemoglobin level, serum iron, serum ferritin and serum zinc but no significant correlation with serum copper (Table 5).

Table (1): Comparison between cases & control regarding some history data

	Cases No = 40		Control No = 40		X^2	Odd (95% CI)	*p*
	No	%	No	%			
Family history of febrile convusion	35	87.5	5	12.5	55.3	13 (4.6 – 36.9)	<0.05
Preterm infant	8	20	6	15	0.556	0.07 (0.0 – 0.2)	>0.05
NICU admission	32	80	26	65	0.133	2.5 (0.8 – 5.9)	>0.05
Hib vaccine	8	20	7	17.5	0.775	1.1 (0.4 -3.6)	>0.05
Positive consanguinity	4	10	5	12.5	0.732	0.78 (0.2 – 3.1)	>0.05
Malnutrition (wt to age <10 centile)	32	80	5	12.5	53.3	12 (4.6 – 36.9)	<0.05

This table shows significant difference between cases and control regarding positive family history of febrile convulsion & malnutrition but no significant differences regarding other history data.

Table (2): Comparison between cases & control regarding vital signs.

	Cases	Control	T	*p*
TEMP(°C) Range Mean±SD	 38.5-40.5 39±0.5	 37.5-39.5 38.5±0.7	 1.3	>0.05
RR(beat/min) Range Mean±SD	 40-60 50.2±5.4	 30-50 44.3±2.3	 1.5	>0.05
HR(beat/min) Range Mean±SD	 130-160 151±23.3	 100-120 112±10.2	 6.3	<0.05

This table shows significant difference between cases and control regarding heart rate but no significant difference regarding temperature & respiratory rate.

Table (3): Comparison between cases & control regarding HB&RDW%

	Cases	Control	t value	*p*
HB(gm/dl) Range Mean±SD	 7-9 8.1±1	 10-13 11.1±1.8	 8.8	 0.00
RDW(%) Mean±SD	 16.8±1.3	 12.7±1.1	 14.2	 0.00

This table shows significant difference between cases and control regarding haemoglobin level in g/dl and RDW%.

Table (4): Comparison between cases & control regarding laboratory data

	Cases No =40	Control No =40	Mann-whiteny test	*p*
Serum iron (µg/dl) Range Median	 30-135 34	 75-200 129	 6.8	 0.00
Serum ferritin (ng/ml) Range Median	 8-80 10	 10-120 46.5	 3.8	 0.00
TIBC(µg/dl) Range Median	 300-500 449	 250-450 316	 5.3	 0.00
Serum Copper (µg/dl) Range Median	 70-200 120	 70-180 93	 3.8	 >0.05
Serum Zinc (µg/dl) Range Median	 20-165 53	 75-130 95	 6.8	 0.00

This table shows significant difference between cases and control regarding iron studies and serum zinc but no significant difference regarding serum copper.

Table (5): Correlations between occurrence of febrile seizure with clinical &lab variables in the studied children(total number=80).

Occurance of febrile seizure	r	*P*
Family history of febrile convulsion	**0.539**	**<0.05**
Preterm history	0.066	>0.05
NICU admission	0.168	>0.05
Hib vaccine	0.032	>0.05
Positive consanguinity	-0.040	>0.05
Malnutrition (wt to age <10 centile)	**0.816**	**<0.05**
Hb	-0.709	0.00
RD	0.850	0.00
S. Ferritin	-0.318	<0.01
S. Iron	-0.761	0.00
TIBC	0.602	0.00
S. Copper	0.149	>0.05
S. Zinc	-0.475	0.00

This table shows significant positive correlations between occurrence of febrile convulsion and presence of positive family history, malnutrition, RDW and TIBC. Also shows statistically highly significant negative correlations between occurrence of febrile convulsion and each of haemoglobin level, serum ferritin, serum iron and serum zinc. No significant correlation with serum copper.

4.Discussion:

Out of our 40 studied children with febrile convulsions, 35 patients had similar condition in the family (87.5%), this is in agreement with **(*Kugler et al., 1998, Herose et al., 2003, Millar, 2006* and *Abou –Khalil et al., 2007*)**. We found in the group of febrile convulsions female: male ratio (1:7), this is in agreement with ***Millar et al, (2006*). *(Baumann, 2008)*** observed that females have a slightly (but definite) higher incidence of febrile seizures while, **(*Aicardi, 1994, Stafstorm, 2002* and *Mollah et al., 2002*)** observed that male children are more prone to febrile seizure than female children. None of history data (prematurity- NICU admission – Hib vaccine- Positive consanguinity) had significant incidence in febrile convulsion group than in control group (***P*>0.05).** Child with body weight <10th percentile were 32 in FC group versus 5 in control group (***p*<0.05)**.This is in agreement with ***Daoud, (2004***) who stated that malnutrition will increase the possibility of simple febrile convulsions. In our study, it was found that there was non significantly higher mean body temperature in cases than controls (39 °C, 38.5°C respectively)(***P* >0.05)**. ***Berg et al., (1995)*, *Varma,(2002)* and *Weng et al., (2010)*** found that the most significant risk factor for the development of a first febrile seizure is the degree of rising of the temperature; the higher the temperature, the higher the likelihood of simple febrile convulsions. In our study, it was found that 8 cases of simple febrile seizures (20%) had a history of preterm labour while (12.5%) of control children were born premature and this is not statistically significant ***p* > 0.05**. This is in agreement with ***Mollah et al., (2002*)** who stated that preterm labour not a risk factor for febrile convulsions. Also, it was found that 32 cases of simple febrile convulsions (80%) had a history of a nursery stay in NICU and 26 controls (65%) had not stay in NICU, this difference not statistically significant ***p*> 0.05**. This is in agreement with ***Amiri et al., (2010).*** while ***Millar, (2006*)** stated that the neonatal nursery stays of more than 28 days will increase the possibility of simple febrile convulsions. Also, it was found that 8 cases (20%) of simple febrile convulsions had a history of Hib vaccine while 7 cases of control children (17.5%) were taken it and this is not statistically significant ***p* > 0.05**.This is in agreement with ***Yeulian S,(2012*)** who stated that no association was found between Hib vaccine and febrile convulsions.. Most cases with febrile convulsions and some of controls showed clinical signs of iron deficiency as pallor, easy fatigability and loss of concentration. In our study, iron deficiency was diagnosed by five criteria i.e. hemoglobin level, red cell distribution width, serum ferritin, iron and TIBC. HB levels ranged from 79 g/dl with mean 8.1. The group of children with fever without febrile convulsions showed mean HB 11.1. The difference between 2 groups was statistically significant (***p*=0.00**). This is in agreement with **(*Pisacane et al., 1996 and Donaldson et al., 2008*).** While **(*Kobrinsky et al., 1995, Daoud et al., 2002 and Bidabadi et al., 2009*)** showed that anemia raises the threshold for febrile convulsions and iron deficiency may protect against the development of febrile convulsions**.** RDW in FC group was significant higher than in control group (16.8 vs 12.7 with (***P*=0.00).** Median levels of serum iron and serum ferritin in FC group (34 µg/dl & 10 ng/dl) respectively were significantly lower than in control group (129 µg/dl - 46.5ng/dl) respectively **P=0.00.** this is in agreement with **(*Naveed-ur-Rehman and Billoo, 2005) and (Dawn, et al.,2009*)** who found lower median serum iron levels (32 µg/dl) than controls(126 µg/dl) with statistically highly significant **(p < 0.01).** In the study by ***Daoud, et al., (2002*),**the significance of iron status as a possible risk factor was evaluated. this is in agreement with **(*Naveed-ur-Rehman and Billoo, 2005) and (Dawn, et al.,2009*)** who found lower median serum iron levels (32 µg/dl) than controls(126 µg/dl) with statistically highly significant **(*p* < 0.01).** In the study by ***Daoud, et al., (2002*),**the significance of iron status as a possible risk factor was evaluated. Similar observations of ferritin were made in a study done by ***Rajwanti et al., (2010).*** Regards trace elements study, Though no obvious clinical manifestation of zinc deficiency was observed in our studied children, serum zinc was significant lower in FC group than control (95 µg/dl,53 µg/dl) respectively ***p* 0. 00**. This is in agreement with, (***Amiri et al., 2010*, *Palliana et al, 2010 and Behrman et al., 2010)*** stated that low selenium and zinc play an important role in the pathogenesis of simple febrile convulsions**.** while ***Garty et al., (1995*)** do not support the hypothesis that febrile convulsion are related to reduced CSF and serum zinc concentration. The current work showed that there was no significant difference in median serum copper levels in cases and controls(120 µg/dl, 93 µg/dl) respectively ***p* > 0.05.** This is in agreement with ***Mishra et al., (2007*)** who found no significant change in serum copper level in cases of febrile convulsion**.** while ***Prasad et al., (2009*)** in their work found that Serum copper levels in children with seizures were significantly increased.

Conclusions:

Serum ferritin and zinc deficiency are risk factor for simple febrile convulsions while serum copper show no significant changes in cases of febrile convulsions.

Recommendation:

Further progressive clinical trials and additional work to discover the full range of functions of iron and zinc in febrile convulsions are needed.

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