

Role of Trace Elements in a sample of Egyptian Children with Febrile Seizures

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Abstract: Background: Febrile seizures is a common neurological problem at childhood. About 30-40 % of children with first episode of febrile seizures will experience recurrences. A number of trace elements are said to play a role in febrile. **Objective:** This study aimed to investigate the association between levels of some trace elements and children with febrile seizures. **Methods:** This case control study was conducted in the neurology department of Al-Azhar university hospitals, Cairo, Egypt for one year. A total of 56 child were included those were divided into 3 groups after fulfilling our inclusion and exclusion criteria. 18 child with febrile seizure (I), 18 child with generalized epileptic seizures (II) and 18 child with febrile illness without seizures (III) as a control group. Serum Zn, Cu and Mg levels were measured. For statistical analysis, SPSS 20 program was used. **Results:** There was significant difference between group I and group II regarding positive family history of siblings with same medical condition. There is no significant differences noted in serum zinc, copper and magnesium levels between each gender. Group I had **lower** levels of zinc than group II with a **significant** difference. While there were no significant differences in copper and magnesium levels between these two groups. Group I had **lower** levels of zinc and **higher** levels of magnesium than group III with a **significant** difference. While there was no significant difference in copper level between groups I and III. Group II had **higher** levels of magnesium than group III with a **significant** difference. While there was no significant difference in zinc and copper levels between group II and group III. **Conclusion:** It appears that the presence of hypozincemia in presence of other risk factors may enhance the occurrence of febrile seizures explaining a possible correlation between low serum zinc levels and febrile seizures. **Recommendation:** Measuring serum zinc should be recommended for all children with febrile seizures. The possibility of prophylactic zinc supplementation in reducing the risk of febrile seizures in children with febrile seizures and even for normal children who are at high risk of developing febrile seizures.

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Keywords: Role; Trace; Element; sample; Egyptian; Children; Febrile; Seizure

1. Introduction

Febrile seizures is a common neurological problem at childhood accounting for 30% of all seizures among children⁽¹⁾. Although described by the ancient Greeks, it was not until the past century that febrile seizures were recognized as a distinct syndrome separate from epilepsy. Febrile seizures has been defined by the American Academy of Pediatrics (AAP) as a seizure 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 febrile seizure⁽²⁾.

About 30-40 % of children with first episode of febrile seizures will experience recurrences, hence febrile seizure is an important illness to understand and prevent⁽³⁾. Febrile seizures occur in young children at a time in their development when the seizure threshold is low. This is a time when young children are susceptible to frequent childhood infections such as upper respiratory infection, otitis media, viral syndrome, and they respond with comparably higher temperatures⁽⁴⁾.

A number of trace elements are said to play a role in febrile seizures by their co-enzyme activity or ability to influence ion channels and receptors. Studies have shown that iron, zinc, selenium, copper and magnesium play significant role in febrile seizure. Zinc acts as a cofactor of glutamic acid decarboxylase, an enzyme which maintains the production of GABA in central nervous system and decreased level of zinc has been observed in febrile seizures⁽⁵⁾.

Magnesium is involved in neuronal function and it inhibits the facilitatory effects of calcium on synaptic transmission and also exerts a voltage dependent blockage of Nmethyl-D-aspartate (NMDA) receptor channel. It is suggested to use supplementary zinc and magnesium as preventive measure for febrile convulsion in children⁽⁶⁾.

Copper inhibits Mg⁺⁺-adenosine triphosphatase (ATPase) and Na⁺-K⁺-ATPase enzymes and disturbs the sodium and potassium homeostasis which results in the genesis of epileptiform discharges⁽⁷⁾.

This study was conducted to investigate plasma levels of trace elements (zinc, copper and magnesium),

among children with febrile seizures to evaluate the relationship between these elements and seizure occurrence.

2. Patients and Methods

This prospective case control study was conducted in the pediatric neurology unit of the neurology department of Al-Azhar university hospitals, Cairo, Egypt for one year period from April 2018 to March 2019. A total of 56 child were included those were divided into three groups. Eighteen child with febrile seizure, eighteen child with generalized epileptic seizures and eighteen child with febrile illness without seizures as a control group. Informed consent was obtained from the parents or guardians. Patients were subjected to thorough history and complete clinical examination. EEG was done to all patients.

Inclusion criteria

1. Children aged between 6 months and 5 years.
2. Normal development children till the time of the study.
3. Fever at least 38°C for febrile groups.
4. Neurologically healthy children before Onset of symptoms for febrile groups.
5. Suffered from generalized seizures according to International league against epilepsy (ILAE) classification 2017⁽⁸⁾ for epileptic group.

Exclusion criteria

1. Children with chronic disease (heart, lung, liver or kidney).
2. Progressive brain disease.
3. Complex febrile seizures.
4. Children with malnutrition and situations that lead to decrease study metals levels in serum including hemolysis, dehydration, vomiting, diarrheal diseases and pneumonia.

Blood samples were taken following a 30-min supine rest, 10 ml blood was withdrawn through a disposable syringe. All samples were centrifuged immediately. The serum was preserved in an Ependorff tubes at -20° for measurement of serum levels of Zn, Cu and Mg with colorimetric method. The normal range serum Zn was 50-120 µg/dl. While the normal range of serum Cu was 80-150 µg/dl and the normal range of Mg was 1.8-2.6 mg/dl. Data was analyzed using SPSS version 20.0. The difference in mean among the groups was assessed by ANOVA and t-test was used to analyze inter group difference. A p-value less than or equal 0.05 was taken as statistically significant.

The study was approved by the ethics committee of the faculty of medicine Al-Azhar University.

3. Results

56 child were included in the study. The mean age of group I and group III was 28.8 and 28 months, respectively while it was 48 months in group II children.

Table (1): Age in different groups.

Groups	Age in months						ANOVA	
	Range			Mean	±	SD	F	P-value
Group I	8	-	54	28.833	±	14.284	12.276	0.001*
Group II	14	-	60	48.000	±	13.758		
Group III	9	-	56	28.056	±	12.964		
Tukey's test								
I & II			I & III			II & III		
<0.001*			0.984			<0.001*		

Male/female distribution was equal in all groups as 44.4 % males and 55.6 % females in each group.

Table (2): Gender distribution in different groups

Gender	Groups							
	Group (I)		Group (II)		Group (III)		Total	
	N	%	N	%	N	%	N	%
Male	8	44.44	8	44.44	8	44.44	24	44.44
Female	10	55.56	10	55.56	10	55.56	30	55.56
Total	18	100.00	18	100.00	18	100.00	54	100.00

There was significant difference between group I and group II regarding positive family history of siblings with same medical condition.

Table (3): Family history of siblings with same medical condition

Family History Same medical condition	Groups					
	Group (I)		Group (II)		Total	
	N	%	N	%	N	%
No	8	44.44	17	94.44	25	69.44
Present	10	55.56	1	5.56	11	30.56
Total	18	100.00	18	100.00	36	100.00

There is no significant differences noted in serum zinc, copper and magnesium levels between each gender.

Table (4): Mean levels of zinc, copper and magnesium for each gender

Variable	Gender						T-Test	
	Male			Female			t	P-value
	Mean	±	SD	Mean	±	SD		
Zinc	61.000	±	22.085	64.467	±	26.812	-0.510	0.612
Copper	93.542	±	22.108	97.867	±	16.811	-0.817	0.418
Magnesium	2.448	±	0.137	2.506	±	0.156	-1.424	0.160

Group I had **lower** levels of zinc than group II with a **significant** difference. While there were no significant differences in copper and magnesium levels between these two groups.

Table (5): Mean levels of Serum Zinc, copper and magnesium in group I and group II

Variable		Groups						T-test	
		Group I			Group II			t	P-value
		Range			Range				
Zinc	Range	28	-	101	33	-	102	-2.104	0.043*
	Mean±SD	49.00	±	22.55	63.72	±	19.299		
Copper	Range	55	-	130	59	-	115	0.807	0.425
	Mean±SD	95.16	±	21.09	90.38	±	13.63		
Magnesium	Range	2.06	-	2.8	2.35	-	2.65	0.973	0.337
	Mean±SD	2.550	±	0.173	2.505	±	0.093		

Group I had **lower** levels of zinc and **higher** levels of magnesium than group III with a **significant** difference. While there was no significant difference in copper level between groups I and III.

Table (6): Mean levels of Serum Zinc, copper and magnesium in group I and group III

Variable		Groups						T-test	
		Group I			Group III			t	P-value
		Range			Range				
Zinc	Range	28	-	101	30	-	134	-3.408	0.002*
	Mean±SD	49.000	±	22.552	76.056	±	25.021		
Copper	Range	55	-	130	63	-	140	-1.008	0.321
	Mean±SD	95.167	±	21.097	102.278	±	21.246		
Magnesium	Range	2.06	-	2.8	2.15	-	2.57	3.274	0.002*
	Mean±SD	2.550	±	0.173	2.385	±	0.126		

Group II had **higher** levels of magnesium than group III with a **significant** difference. While there was no significant difference in zinc and copper levels between group II and group III.

Table (7): Mean levels of Serum Zinc, copper and magnesium in group II and group III

Variable		Groups						T-test	
		Group II			Group III			t	P-value
		Range			Range				
Zinc	Range	33	-	102	30	-	134	-1.656	0.107

	Mean±SD	63.722	±	19.299	76.056	±	25.021		
Copper	Range	59	-	115	63	-	140	-1.998	0.054
	Mean±SD	90.389	±	13.630	102.278	±	21.246		
Magnesium	Range	2.35	-	2.65	2.15	-	2.57	3.259	0.003*
	Mean±SD	2.505	±	0.093	2.385	±	0.126		

4. Discussion

Febrile seizures is a common neurological problem at childhood accounting for 30% of all seizures among children ⁽¹⁾. A number of trace elements are said to play a role in febrile seizures by their co-enzyme activity or ability to influence ion channels and receptors. Studies have shown that iron, zinc, selenium, copper and magnesium play significant role in febrile seizure ⁽⁹⁾.

The mean age of febrile seizure children and febrile children has a significant difference with the epileptic children but this could be attributed to the epilepsy type of these children and its age distribution ⁽¹⁰⁾.

Family history of the same condition was present in 55% of children with febrile seizures in this study. This is more than that in the epileptic group which was only 6%. This is also more when compared other studies like Lakshmi S, in which family history of febrile seizures was about 10% ⁽¹¹⁾.

Farwell et al reported 29% positive family history in his study ⁽¹²⁾. Baek SJ et al reported 14% positive family history in his study ⁽¹³⁾. Kumari, Margaretha and Kafadar reported 44%, 48%, 26% of positive family history respectively ^(14, 15, 16).

However family history of febrile seizure in this study is less when compared to some studies like this of Iman Abd El Rehim Mohamed Aly and her colleagues in which family history of febrile seizures was about 87% ⁽¹⁷⁾.

All these studies revealed that occurrence of febrile seizure in children with positive family history (which account for the rule of family history in febrile seizures). Serum zinc, copper and magnesium levels did not show any significant difference between genders. All the previous studies have shown similar findings in this aspect ^(11, 13, 18, 19, 20, 21, 22).

Serum zinc levels in children with febrile seizures was found to be significantly lower than that of the epileptic children. Jun-Hwa Lee, M.D. and Jeong Hyun Kim, M.D. compared serum zinc levels in patients with febrile and afebrile convulsions; they concluded that compared to patients with afebrile convulsions, patients with febrile convulsions had lower serum zinc levels ⁽²³⁾.

Gündüz Z et al. study and Saghazadeh et al on their meta-analysis also reported the same result ^(24, 25). Serum magnesium and copper levels in children with febrile seizures was found to have no significant

difference with those of epileptic children. Amene Saghazadeh and co-workers concluded on their meta-analysis that no changes in copper or magnesium concentrations were linked to epilepsy in comparison to febrile seizures ⁽²⁵⁾.

However Bharathi S and Chiranjeevi K found that there is statistically significant association with hypomagnesaemia and ‘Typical Febrile convulsions’ No such association was found with epileptic convulsions ⁽²⁶⁾.

Serum zinc levels in children with febrile seizures was found to be significantly lower than that of the febrile children without seizures “which considered as control group”. These results were matching the results of many studies done before. Najmus Saqib and Mahvish Qazi reported in their study that there is a relation between serum zinc and simple febrile seizures. Serum zinc level was significantly lower in children with simple febrile seizures in comparison with febrile children without seizure ⁽²⁷⁾.

Also Sreenivasa B et al, Karthikeyan P et al, Khajeh A et al, Sampathkumar P and Kannan KS., Salehionran MR et al and Gattoo I et al Reported the same results ^(27, 5, 28, 29, 30, 31).

There was no significant difference in serum copper levels between children with febrile seizures and those with only febrile illness. Sawsan Issa Habeeb reported in her study that the mean serum copper level don’t show significant difference between patients with febrile seizure and those with febrile illness alone ⁽¹⁸⁾.

Similar result was concluded by Mahyar et al. And Amiri et al. ^(33, 22) Shokrzadeh M and his co-workers observed that meaningful higher serum Copper level in febrile seizure children when compared to children with febrile illness alone ⁽¹⁹⁾.

Serum magnesium levels in children with febrile seizures was found to be significantly higher than that of the children with only febrile illness. However other studies like Baek SJ et al and Namakin K et al found that hypomagnesaemia was more common in patients with febrile seizure than in those with febrile illness alone ^(13, 20).

On the other hand studies like Lakshmi S et al, Khosroshahi N et al and Sepideh Amouian with his colleagues reveals that there is no association between levels of serum magnesium and febrile seizures when compared to febrile illness only ^(11, 34, 21).

Conclusion

Low serum zinc level in the group of patients with febrile seizures compared with the two other groups which indicate the existence of a relationship between the serum zinc level and development of febrile seizures. There is no significant association between copper and magnesium levels and febrile seizures or epilepsy. There was higher magnesium levels in epileptic and febrile seizures groups compared with the febrile illness only group. It appears that the presence of hypozincemia in presence of other risk factors may enhance the occurrence of febrile seizures explaining a possible correlation between low serum zinc levels and febrile seizures.

Recommendations

Measuring serum zinc should be recommended for all children with febrile seizures. The possibility of prophylactic zinc supplementation in reducing the risk of febrile seizures in children with febrile seizures and even for normal children who are at high risk of developing febrile seizures. Further progressive clinical trials and additional work should be done to discover the relationship between magnesium and seizures and also zinc, copper and magnesium with epilepsy. Future research should be directed towards the therapeutic trial of zinc supplementation and formulate the zinc treatment regimen including its dose and duration.

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