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DETERMINATION OF ZINC LEVEL AND CATIONS CROSS THE CELL MEMBRANE IN SERUM OF IRAQI CHILDREN WITH FIRST FEBRILE SEIZURES

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ABSTRACT

Background: Many research works clearly indicate that febrile seizure is the most common type of clinical problem in children that usually occurs at <6 years. The objective of the present study was to find the changes in serum zinc level (males and females) children and the role of cations cross the cell membrane which included sodium, potassium, and calcium in prediction of first febrile seizure within the first 24 hours. In addition to find if there was any correlation between Zn level with the other parameters mentioned in current work. **Methods:** A total of 64 children (30 male and 34 female) aged between 1 month to 6 years were included as patients group. Thirty two healthy children were selected as the control group, their age range was comparable with that of the patients. Serum level of zinc was measured by the graphite furnace flame atomic absorption spectrophotometry. Serum levels of sodium, potassium, calcium were measured using Electrolyte Analyzer. Blood glucose concentration was measured by the Reflotron Plus technique. The comparisons between groups were done using SPSS statistical program. **Results:** There was no significant difference in age ($P>0.05$). There was a significant difference between the groups regarding temperature at the time admission. A high significance decrease ($p<0.01$) in the mean level of calcium and zinc , a high significance increase ($p<0.01$) in the mean level of blood glucose and sodium, while no significant changes in potassium level in patients were noticed compared with control group. Serum zinc level was high significance decrease ($p=0.005$) in group male patients compared to female patients. **Conclusion :** Based on our data, it was revealed that the parameters such as age, gender, body temperature, low zinc levels, and low calcium levels are among the risk factors in occurrence of the first febrile. Therefore, we suggest that deficiencies of serum zinc and calcium levels may be responsible for the pathogenesis of first febrile seizure in children.

KEYWORDS: Febrile Seizures, serum zinc, serum calcium, cations.

INTRODUCTION

The most common neurologic finding in children is convulsion. There are several types of convulsion, but the most common type of the disease is the febrile seizures observed as simple and complex febrile seizures.[1] Seizures with fever occur in 3% to 5% of children in North America and Europe and in up to 14% of children of Asian origin.[2] Various factors were described in the pathophysiology of febrile seizures like bacterial and viral infections.[3] susceptibility of the immature brain to temperature[4], association with interleukins[5], circulating toxins[6], trace element deficiency[7] and iron deficiency.[8] Role of trace elements like selenium, magnesium, copper and zinc were described in association with febrile seizures.[9] Trace elements appear to play a role by their ability to modulate neurotransmission by acting on ion channels and their coenzyme activity. Blood glucose measurement is essential, and any further laboratory testing should be requested as necessary according to clinical condition and diagnostic hypothesis.[9] Serum and urinary Ca levels were previously studied in children with FS.[10,11] Critical illness is associated with decreased serum total and ionized Ca levels, which are correlated with the severity of the underlying disease.[11] Sodium (Na+) is the major cation of extra cellular fluid and as such plays a central role in the maintenance of the normal distribution of water and osmotic pressure in various fluid compartments.[12] Potassium (K+) on the other hand is the major intracellular cation, having an average cellular concentration in tissue cells of 150 mmol/L.[13] In addition to water balance, these electrolytes play an important role in maintenance of pH, regulation of heart and muscle function, electron transfer reactions as well as serving as cofactors for enzymes.[14] Zinc is an important micronutrient that plays a significant role in growth and development, immune system response, enzymatic activity of different organs, proteins and cellular metabolism, neurological functions, nerve impulse transmission and hormone release.[15,16] The

possible role of zinc deficiency in provoking febrile seizures were reported in different studies.[17,18] In addition, zinc significantly reduces the severity of illness and the duration of fever in children with pneumonia and diarrhea by the activation of immune enhancing T-cells.[19] As part of our efforts in this study is to examine the role of serum sodium, potassium, calcium, zinc levels in prediction of first febrile seizure within the first 24 hours.

SUBJECTS AND METHODS

Subjects

Sixty four children (30 male and 34 female) with first seizures convulsion participated in the study. The included patient's age range was between 1 months - 6 years. The patients were recruited from the Al- Alalwiya Children Teaching Hospital in Baghdad capital, Iraq from October 2014 to April 2015, (Figure 1). Blood sampling was performed, when the seizure attack elapsed (within the first hour of the attack) in the morning between 8:00 and 10:00 am. Blood sampling (3 mL) was centrifuged at 1500 xg for 10 min, and the serum was stored at -20ºC until the time of analysis. All children with febrile convulsions were at least 24 hours seizure-free from the sampling time. This study excluded patients with well-known history of epilepsy. This study also excluded the patients who were taking Ca or Zn supplements. Moreover, patients with any evident major systemic diseases, including diabetes mellitus, cardiovascular diseases, or other endocrine disorders, were excluded as well. Thirty two healthy children were selected as the control group. Their age range was comparable with that of the patients. None of these control subjects had any systemic or endocrine disorders. A complete clinical investigation was performed by a specialized pediatrician. The consent were obtained from their first degree relatives (mother or father) and informed that the results of the study will be given to them as a free useful laboratory tests. The conditions of the Ethics Committee of the Al-Mustansiriya university, college of science, chemistry department were followed in the study.

Figure 1: Baghdad province, the capital of Iraq.

METHODS

Blood glucose concentration (mmol/L) was measured by the Reflotron Plus technique. Calcium, sodium, and potassium concentration (mmol/L) were measured using Electrolyte Analyzer (Roche). Serum zinc concentration was measured by the graphite furnace flame atomic absorption spectrophotometry (AA 300 pc, German-Analytic Jena) technique. Serum zinc concentration was reported as µg/dL.

BIOSTATISTICAL ANALYSIS

The results were expressed as mean ± standard deviation for normally distributed variables. Statistical analysis was performed using LSD, considering $p< 0.05$ as the lowest limit of significance. Student t-test was used to compare the patients and the control group. Pearson's correlation coefficients (r) were calculated to estimate the correlation between the parameters. All statistical analysis was performed using SPSS Statistics Program version 17, USA.

RESULTS

The aim of this study is to find the changes in serum zinc level (males and females) children and the role of cations cross the cell membrane which included sodium, potassium, and calcium in prediction of first febrile seizure within the first 24 hours. In addition to find if there is any correlation between Zn level with the other parameters mentioned entities above. Table 1 represents the number, percentage and gender distribution of patients and control groups, Also shows that females predominated in patients group.

Table 1: Gender distribution in children with febrile seizures and control groups

Groups	Male		Female		Total	
	N	%	N	%	N	%
Febrile convulsion N= 64	30	46.88	34	53.12	64	100%
Control N= 32	20	62.5 %	12	37.5 %	32	100%

Table 2: Comparison between patients & control regarding laboratory data

Parameters	Patients N=64		Control N= 32		p value
	mean	SD	mean	SD	
Age (months)	21.77	24.56	17.23	19.42	0.314
Temp. on Admission (^{0}C)	37.65	6.34	37.00	0.00	0.047*
Blood glucose (mmol/L)	8.45	5.28	4.45	0.71	0.0001**
Serum Calcium (mmol/L)	1.08	0.15	1.26	0.05	0.0001**
Serum Sodium(mmol/L)	139.75	7.24	139.50	2.67	0.001**
Serum Potassium (mmol/L)	4.24	0.69	4.67	0.52	0.149
Serum Zinc (µg/dL)	59.97	20.49	86.54	34.45	0.01**

***: Significant difference (p<0.05) **: highly Significant difference (p≤0.01)**

Table 2, represents the mean, and SD for each of Age, temperature, blood glucose, blood calcium, serum sodium, serum potassium, and serum zinc levels in the both groups. The minimum age in children with febrile seizures (patients group) was 1 months and the maximum 70 months and a mean of 21.77± 24.56 months. Similarly, the minimum, maximum, and mean age among the control group was 1, 72, and 17.23±19.42, respectively. There was no significant difference between two groups regarding the age (p= 0.314). The mean serum potassium level was 4.24 ± 0.69 in simple febrile seizure and 4.67± 0.52 in control group with no significance differences between two groups, statistically (p= 0.149). The mean body temperature on admission in patients and control groups was 37.65 ± 6.34 and 37.0 ± 0.00, respectively. Regarding the body temperature, a significant difference was observed between two groups (p= 0.047). The results show a highly significance increase (p=0.0001) in the mean level of blood glucose 8.45 ± 5.28 in patients as compared to mean control group 4.45± 0.71. The mean sodium was 139.75±7.24 in patients and 139.50 ±2.67 in control groups, a highly significance increase was observed between two groups (p=0.001). There was a highly significance decreased (p= 0.0001)in the mean levels of calcium 1.08±0.15 in patients group compared to control group 1.26 ±0.05. Serum zinc level was highly significant decreased (p=0.01) in patients group (59.97±20.49) compared with the control group (86.54±34.45).

Table 3: Comparison between males and females patients groups

Parameters	Males children N=30		Females children N=17		P value
	mean	SD	mean	SD	
Age (months)	29.07	26.82	15.35	21.09	0.369
Temperature(^{0}C)	36.28	9.21	38.85	0.48	0.045
Blood glucose (mmol/L)	7.19	4.47	9.55	5.81	0.408
Serum Calcium (mmol/L)	1.02	0.11	1.12	0.17	0.037
Serum Sodium(mmol/L)	139.33	5.60	140.12	8.59	0.138
Serum Potassium (mmol/L)	4.23	0.51	4.24	0.84	0.034
Serum Zinc (µg/dL)	53.43	12.54	60.85	22.12	0.005

***: Significant difference (p<0.05) **: highly Significant difference (p<0.01)**

Table 3, represents the comparison of all measured parameters which used in this study, between males and females patients groups. No significant differences (p>0.05) in age, blood glucose, and serum levels of sodium between males and females patients groups. There was statistically significant difference between the two groups in body temperature, calcium and potassium. While there was highly significant differences in serum levels of zinc (p=0.005) between males and females patients groups.

Table 4: Comparison between males patients and males control groups

Parameters	Males patients N=30		Males controls N=20		P value
	mean	SD	mean	SD	
Age (months)	29.07	26.82	12.45	13.35	0.044
Temperature(^{0}C)	36.28	9.22	37.00	0.50	0.018
Blood glucose (mmol/L)	7.19	4.47	4.42	0.67	0.0001

Blood Calcium (mmol/L)	1.02	0.11	1.26	0.05	0.017
Serum Sodium(mmol/L)	139.33	5060	139.73	2.89	0.123
Serum Potassium (mmol/L)	4.23	0.51	4.68	0.49	0.919
Serum Zinc (µg/dL)	53.43	12.54	84.21	27.27	0.050

***: Significant difference (p<0.05) **: highly Significant difference (p<0.01)**

The comparison between males patients and males control groups is presented in Table 4. No significant difference (p>0.05) in serum levels of sodium and potassium between the two groups. In the present study, there is significant differences (p<0.05) in age, body temperature, calcium and serum zinc. The comparison between males patients and males control groups showed a highly significant difference (p=0.0001) in blood levels of glucose.

Table 5: Comparison between females patients and females control groups

Parameters	Females patients N=34		Females controls N=12		P value
	mean	SD	mean	SD	
Age (months)	15.35	21.09	25.91	25.78	0.225
Temperature(^{0}C)	38.85	0.48	37.00	—	0.0001
Blood glucose (mmol/L)	9.55	5.82	4.52	0.80	0.002
Blood Calcium (mmol/L)	1.12	0.17	1.27	0.07	0.011
Serum Sodium(mmol/L)	140.11	8.59	139.09	2.26	0.012
Serum Potassium (mmol/L)	4.24	0.84	4.64	0.60	0.166
Serum Zinc (µg/dL)	60.85	22.13	67.91	11.72	0.008

***: Significant difference (p<0.05) **: highly Significant difference (p<0.01)**

Table 5, represents the comparison between females patients and females control groups. No significant difference (p>0.05) in age, and serum levels of potassium between the two groups. Highly significant differences (p<0.01) in body temperature, blood glucose, serum calcium, serum sodium and serum zinc.

DISCUSSION

Febrile seizure is a common neurologic problem occurring in children aged between 1 months to 6 years. The etiology of febrile seizure is unknown but genetic factors, trace elements or electrolyte disturbances may have a role in its occurrence. To date it is revealed that febrile seizures can be induced by several factors. It is generally believed that an FS is an age-dependent response of the immature brain to fever.

Out of our 64 studied children with febrile seizures, it was found that the group of febrile convulsions female: male ratio about (1:1), this is in not agreement with several studies, which find that the group of febrile convulsions female: male ratio was (1:7).[20,21] Baumann, (2008) observed that females have a slightly (but definite) higher incidence of febrile seizures[22] while, Aicardi, 1994, Stafstorm, 2002 and Mollah *et al.*, 2002 observed that male children are more prone to febrile seizure than female children.[23,24,25] The difference of this result with other previous studies may be due to the in samples size between two groups. In this study, it was found that there was significantly higher mean body temperature in group of febrile seizures than control group (p <0.05). Several studies 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 likelihood of simple febrile seizures, the higher the temperature.[21,26,27] In this study, results show that blood glucose levels are often raised during or soon after a seizures. it was found that there was significantly higher mean of blood glucose in male and female patients of febrile seizures than control group (p <0.01). Results show that blood glucose levels are often raised during or soon after a seizure. The hyperglycaemia is only transient. Probably a seizure produces an increase in circulating level of both cortisol and adrenaline and these raise blood glucose levels by their anti-insulin action. Its existence must be recognized, as a mistaken diagnosis of diabetes mellitus may be made.[28] In the present study also low levels of serum calcium were observed in febrile seizures patients when compared to control group (p<0.05). Calcium is an essential element that plays a major role in the normal functioning of neurons and at neuromuscular junction. Due to the depolarization, the excitability of neurons increases the extra cellular glutamate concentration reflecting increased intracellular neuronal calcium which further depolarizes the cell leading to neuronal injury and or death under conditions of excessive neuronal activation.[29] The mechanism suggested for lower calcium levels or hypocalcaemia leading to the development of seizures is that hypomagnesaemia causes serum calcium levels to decline in a significant way by impairing the synthesis or secretion of parathyroid hormone[30,31] and together they produce a membrane state of hyper excitability of neurons, which have been found to be associated strongly with seizures in adults and children.[32] Natelson *et al.*, (1979) assumed that the release of hormones, epinephrine and corticotrophin during stress, contributes to low levels of serum calcium just before a seizure.[33] A significant high levels of sodium was observed in the patients group with simple febrile seizure as compared to control group (P =0.001).

There was significant difference in the mean serum sodium between the patients group and controls. Nadkarni et al., (2011) found that measurement of the serum sodium in a child with febrile seizures helps in predicting seizure recurrence within the same febrile illness.[34] Non significant decreased levels of potassium was observed in patients group with febrile seizures than control group. No significant difference in potassium level was observed between male patients with control as well as between female patients with control, while a significant difference was found between male patients and female patients. Potassium abnormalities unlike other electrolyte abnormalities, hypokalemia or hyperkalemia rarely cause symptoms in the central nervous system, and seizures do not occur. Changes in the extracellular potassium serum levels exert their effects mainly on the function of the cardiovascular and neuromuscular systems. Severe potassium abnormality may therefore provoke fatal arrhythmias or muscle paralysis before CNS symptoms appear.[35] Zinc has a regulatory effect on glutamic acid decarboxylase and the synthesis of Gammaaminobutyric acid, which is an important inhibitory neurotransmitter. Attempts were done to identify predisposing risk factor like gender, axillary temperature and metabolic disturbance (especially serum zinc, glucose, calcium, sodium, potassium). This knowledge has a practical value and advising parents regarding recurrent seizures. The current work showed that serum zinc level was highly significant decreased in patients group than with the control group. While there was highly significant differences in serum levels of zinc between males and females patients groups. Under normal physiological conditions zinc and other trace elements have been found to modulate the neuronal excitability. Low levels of serum zinc have also been reported in children with febrile seizures.[36,37,38] This result is in agreement with, (Amiri et al., 2010, Palliana et al, 2010 and Behrman et al., 2011) stated that low zinc play an important role in the pathogenesis of simple febrile convulsions.[39,40,41] Serum zinc deficiency is a risk factor for simple febrile seizures. This work also supported by Mohamed Aly *et al.*, (2014) who found that serum ferritin and zinc deficiency are risk factors for simple febrile convulsions.[42] While Garty et al., (1995) do not support the hypothesis that febrile convulsion are related to reduced CSF and serum zinc concentration.[43] The serum zinc levels did not show any significant correlation with age, gender, axillary temperature and metabolic disturbance in children with seizure in our study. Several previous studies have shown similar findings in this aspect.[44]

CONCLUSION

The parameters which used in this work such as age, gender, body temperature, low zinc levels, and low calcium levels are among the risk factors in occurrence of the first febrile. Therefore, we suggest that deficiencies of serum zinc and calcium levels may be responsible for the pathogenesis of first febrile seizure in children. Further study must be done on antioxidant vitamins and trace element. Increase awareness of the family may be remove these risk factors, also zinc and/or calcium supplementation can be given in febrile seizure, and, thus, could lead to a decrease in incidence of febrile seizures.

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