

## RISK OF LOW SERUM MAGNESIUM IN FEBRILE SEIZURES

By

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### ABSTRACT

**Background:** Febrile seizures defined as seizures that occurs between the age of six and sixty months, with a temperature of 38 degree 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 afebrile seizures. One of the important things in febrile seizures that are discussed is the status of serum magnesium in children with febrile seizures and it was mentioned that the risk of febrile seizures increased with low serum magnesium in children. A seizure is a paroxysmal alteration of neurologic function caused by the excessive, hyper- synchronous discharge of neurons in the brain. Epileptic seizure is used to distinguish a seizure caused by abnormal neuronal firing from a nonepileptic event, such as a psychogenic seizure. Epilepsy is the condition of recurrent, unprovoked seizures.

**Objective:** To investigate the status of serum magnesium in children with febrile seizures compared to controls.

**Patients and Methods:** This is a case control study that was conducted on children with febrile seizures in Imbaba general hospital and El-Hussein university hospital during the period from 1st of May 2018 to last of March 2020. The study was carried out on 50 children aged between 6 months and 5 years old presented with febrile seizure and 50 Children with fever without seizures in the emergency as a control group cross matched regarding age and sex.

**Results:** Magnesium (Mg) level decreased significantly in case study when compared with control (Mg;  $1.54 \pm 0.48$  mg/dl versus  $2.05 \pm 0.27$  mg/dl) with statistically significant difference also Calcium (Ca) level decreased significantly in case study (Ca;  $8.69 \pm 0.42$  mg/dl versus  $9.14 \pm 1.11$  mg/dl) and lastly potassium level (K) decreased significantly in case study ( $4.08 \pm 0.38$  mg/dl versus  $4.39 \pm 0.54$  mg/dl) while associated with insignificant decrease of sodium level (Na) in case study ( $138.32 \pm 2.58$  mg/dl versus  $138.83 \pm 1.95$  mg/dl), respectively.

**Conclusion:** Magnesium level decreased significantly in cases with febrile convulsion when compared with children with fever without convulsion.

**Keywords:** Magnesium; Seizures; Febrile seizures.

## INTRODUCTION

Febrile seizure (FS) is the most common type of seizures it occurs in children between the ages of 6 months to 5 years with body temperature over 38 ° C and without any infection such as meningitis and encephalitis in the central nervous system. The incidence of Fs is 5 cases per 1000 children annually<sup>1</sup> Two four percent of children experiences FS during the first 6 years of life and almost one third of them have been experienced recurrent episodes. Therefore, identification of these risk factors appears to be necessary to prevent recurring attacks<sup>2</sup>.

Febrile seizures are classified into two groups including simple and complex seizures. Simple seizures happen with generalized tonic-clonic movements for less than 15 minutes without recurrence in the first of 24 hours. Complex seizures occur more than once in 24 hours for more than 15 minutes and are focal<sup>3</sup>.

Magnesium is obtained from whole grains, soft drink, nuts, and green leafy vegetables. However, global diet trends are moving towards high consumption of low magnesium processed food<sup>4</sup> People who eat such diets are more likely to develop a

magnesium deficiency, as are those who cook or boil all foods—especially vegetables, those who drink soft water, and those who eat food grown in magnesium-deficient soils, where synthetic fertilizers containing no magnesium are often used<sup>5</sup>.

Magnesium may modulate seizure activity by antagonizing excitatory calcium influx through N-methyl-D-aspartate (NMDA) receptor<sup>6</sup>. In febrile seizure, which afflicts 2–5% of the pediatric population and is the most common seizure disorder in children, only one third of patients have a positive family history of febrile seizure or epilepsy, and most patients with febrile seizure have no evident risk factors<sup>7</sup>.

**This study aims to** investigate the status of serum magnesium in children with febrile seizures compared to controls.

### **Ethical consideration:**

1. Approval of ethical committee, Faculty of Medicine Al-Azhar University.
2. Written consents from parents of the patients.
3. The patients have the right to withdraw from the study at any time.

4. All the obtained data are confidential, and the patients have the right to keep them.
  5. The authors declare that there is not any financial support regarding the research and publication.
  6. No conflict of interest regarding the study and publication.
3. Convulsion:
    - Type (Simple - Complex)
    - Frequency (One to two times in 24 hours)
    - Regarding control temperature  $\geq 38\text{ c}^\circ$  without fits.
    - Duration (Less than 15 minutes).

### **PATIENTS AND MATERIALS**

This is a case control study that was conducted on children with febrile seizures in Imbaba general hospital and El-Husseein university hospital during the period from 1st of May 2018 to last of March 2020. The study was carried out on 50 children aged between 6 months and 5 years old presented with febrile seizure & age and sex matched controls of 50 Children with fever without seizures in the emergency room.

#### **Inclusion Criteria:**

**Cases:** Cases are defined as seizures that occur between the age of 6 and sixty months, with a temperature of  $38^\circ\text{ C}$  or higher, that are not the result of central nervous system infection or any metabolic imbalance.

1. Age of 6 and sixty months.
2. Temperature  $\geq 38\text{ c}^\circ$ .

4. Post ictal state less than 2 hours.
5. No Neurological evidence of IEM and neurodegenerative disease.

#### **Exclusion criteria:**

1. Children with gastroenteritis or dehydration.
2. Children with suspected CNS infection.
3. Developmental delay.
4. Metabolic or neurological problems.
5. Renal or endocrinal diseases.

**All the studied cases were subjected to the following:**

1. **Thorough history taking:** Stressing on temperature, tachypnea, vomiting, diarrhea, triggering factors for the febrile episode like cough and cold, nasal discharge, ear discharge, burning micturition

or crying during micturition, family history of seizures, developmental history and recurrent attack also recorded.

## 2. Thorough clinical

**examinations:** Stressing on vital data, axillary temperature, blood pressure, signs of respiratory distress, capillary refill time, peripheral pulsation. General examination to exclude IEM, CNS examination for signs of meningeal irritation and systemic examination for other systems.

## 3. Blood sample:

- Total serum magnesium, calcium, sodium, and potassium are measured using Bio Systems BTS-350, Costa Brava.
- Complete blood count using ERMA, PCE-210N.
- Renal function test using Bio Systems BTS-350, Costa Brava.

- Liver function tests are measured using Beckman Synchron CX5 system, ERMA.

**Statistical analysis:** The collected data were organized, tabulated, and statistically analyzed using statistical package for social sciences (SPSS) version 19 (SPSS Inc, Chicago, USA), running on IBM compatible computer. For qualitative data, frequency and percent distributions were calculated. For quantitative data, mean, standard deviation (SD), minimum and maximum were calculated. For comparison between two groups, the independent samples (t) test was used. Pearson correlation coefficient (r-test) was used for correlating different variables. For all tests p value  $<0.05$  were considered significant. For all tests p value  $>0.05$  were considered insignificant.

## RESULTS

Our result will be demonstrated in the following tables.

**Table (1): Demographic data of both studied group**

Parameters	Patient group	Control group	T test	P value
Age (years)	2.45±1.01	2.54±1.23	0.430	0.660
Sex				
Male	26 (52.0%)	24 (48.0%)	0.400	0.690
Female	24 (48.0%)	26 (52.0%)		
Family history	28 (56.0%)	18(36.0%)	4.026	0.045
positive Negative	22 (44.0%)	32 (64.0%)		
Birth order	4 (2 – 5)	5 (2 – 5)	-0.351	0.725
Mother education and occupations				
No	25 (50.0%)	22 (44.0%)	0.361	0.548
Yes	25 (50.0%)	28 (56.0%)		

This table shows significant deference regarding family history while insignificant deference regarding Age, sex,

birth order and mother education and occupations between both studied groups.

**Table (2): Clinical finding in both studied group**

Parameters	Patient group	Control group	T test	P value
Weight (Kg)	12.3±2.51	12.6±2.87	0.67	0.51
Height (Cm)	86.5±11.24	88.98±11.34	1.07	0.28
Weight / Height	0.143 ± 0.05	0.146 ± 0.09	0.206	0.837
Seizures	Simple	44 (88.0%)	0 (0.0%)	--
	Complex	6 (12.0%)	0 (0.0%)	
Temperature (°c)	39.03±0.16	38.92±0.28	2.49	0.06

This table shows insignificant deference regarding the parameters, weight, height,

weight/ height, seizures, and temperature between both studied groups.

**Table (3): Laboratory finding in both studied groups**

Parameters	Patient group	Control group	T test	P value
WBCs (10 <sup>9</sup> /l)	7.2±2.72	8.67±3.59	2.28	0.02
Lymphocyte (%)	40.71±12.45	28.81±14.11	4.41	<0.001
RBCs (10 <sup>12</sup> /l)	4.53±0.49	4.17±0.62	3.09	0.003
Hemoglobin (g/dl)	10.85±1.72	11.96±1.09	3.85	<0.001
Magnesium (mg/dl)	1.54±0.48	2.05±0.27	6.31	<0.001
Calcium (mg/dl)	8.69±0.42	9.14±1.11	2.65	0.009
Sodium (mg/dl)	138.32±2.58	138.83±1.95	1.09	0.27
Potassium (mg/dl)	4.08±0.38	4.39±0.54	3.31	0.001
<b>Renal and Liver Functions:</b>				
Creatinine (mg/dl)	0.75±0.21	0.68±0.18	1.56	0.06
BUN (mg/dl) AST (mg/dl)	13.0±3.73	12.79±3.69	0.28	0.77
	21.18±7.6	20.46±7.61	0.46	0.65
ALT (mg/dl)	23.86±7.71	23.53±7.82	0.21	0.84

This table shows significant deference regarding hemoglobin, magnesium, calcium, potassium, lymphocyte, and RBCs while

insignificant deference regarding other parameters in both studied groups.

**Table (4): Correlation between types of seizures and clinic-laboratory findings in studied groups**

Parameters	Simple seizure (24)	Complex seizure (26)	T test	P value
Age (years)	2.23±1.14	2.64±0.85	1.47	0.15
Weight (Kg)	11.76±2.84	12.75±2.14	1.42	0.16
Length (Cm)	84.52±13.1	88.18±9.29	1.15	0.25
Temperature (°c)	38.89±0.29	38.94±0.26	0.57	0.56
WBCs (10 <sup>9</sup> /l)	7.41±2.67	7.03±2.81	0.48	0.63
Neutrophil (%)	53.19±13.46	48.74±10.41	1.31	0.19
Lymphocyte (%)	39.15±13.33	42.04±11.75	0.82	0.42
RBCs (10 <sup>12</sup> /l)	4.53±0.43	4.52±0.55	0.001	0.99
MPV (fL)	8.44±0.81	8.39±1.07	0.16	0.87
Hemoglobin (g/dl)	11.99±0.79	11.94±1.31	0.18	0.86
Creatinine (mg/dl)	0.72±0.2	0.76±0.21	0.76	0.45
BUN (mg/dl)	12.87±3.86	13.11±3.68	0.23	0.82
AST (mg/dl)	22.31±7.87	20.22±7.43	0.96	0.34
ALT (mg/dl)	24.43±8.14	23.37±7.43	0.48	0.63

This table shows that the type of the types of seizures has no significant effect on clinical and laboratory data of studied group.

**Table (5): Correlation between types of seizure and Serum Electrolyte Levels in studied groups**

Parameters	Simple seizure	Complex seizure	T test	P value
Magnesium (mg/dl)	1.54±0.44	1.53±0.53	0.08	0.94
Calcium (mg/dl)	8.63±0.41	8.75±0.44	1.02	0.31
Sodium (mg/dl)	138.57±2.98	138.11±2.22	0.616	0.54
Potassium (mg/dl)	4.09±0.39	4.06±0.38	0.22	0.82

This table shows no significant effect of seizure types on serum Electrolyte Levels in studied groups.

**Table (6): Correlation between Serum Electrolyte Levels of the Patient group**

	Mg		Ca		Na		K	
	R	p	r	P	R	p	r	P
Mg	--	--	0.84	0.001*	0.07	0.61	0.05	0.75
Ca	0.84	0.001*	--	--	0.02	0.92	-0.04	0.74
Na	0.07	0.61	0.02	0.92	--	--	0.08	0.56

This table shows that cases with febrile seizure have significant positive correlation between Mg and Ca, while insignificant correlation with other electrolyte levels (NA and K).

**Table (7): Correlation between Serum Electrolyte Levels of the Simple Febrile seizure of the Studied Cases**

	Mg		Ca		Na		K	
	R	p	r	P	r	p	r	p
Mg	--	--	0.87	0.001*	0.27	0.22	0.11	0.63
Ca	0.87	0.001*	--	--	0.15	0.51	-0.11	0.62
Na	0.27	0.22	0.15	0.51	--	--	0.12	0.59

This table shows that cases with simple febrile seizure has significant positive correlation between Mg and Ca, while insignificant correlation with other electrolyte levels (NA and K).

**Table (8): Correlation between Serum Electrolyte Levels of the Complex Febrile seizure of the Studied Cases**

	Mg		Ca		Na		K	
	R	p	r	P	r	p	r	P
Mg	--	--	0.83	0.001*	0.38	0.05	0.06	0.97
Ca	0.83	0.001*	--	--	0.22	0.26	-0.14	0.48
Na	0.38	0.05	0.22	0.26	--	--	0.33	0.08

This table shows that cases with complex febrile seizure has significant positive correlation between Mg and Ca, while

insignificant correlation with other electrolyte levels (NA and K).

### **DISCUSSION**

Febrile seizures (FS) are the most common cause of seizures among children. It has been known since ancient times that seizures frequently accompany fever in young children. The exact pathogenesis is unknown but involves factors such as genetic predisposition and alterations<sup>8</sup>.

Magnesium (Mg) is the fourth most common cation in the body and third most common intracellular cation. It is mainly found in muscle, other soft tissues, bone, and erythrocyte<sup>9</sup>.

This study aimed to investigate the status of serum magnesium in children with febrile seizures compared to controls.

In the present study, age, weight, and length were nearly comparable between studied cases as shown in Table (1) and (2).

These results agreed with **Namakin et al.**<sup>10</sup> who reported that the mean age of infant with febrile seizure between 20 and 27 months.

In the present study, there were 26 case (52.0%) male in study case versus 24 (48.0%) in control case and there were 29 case (58.0%) with positive family history in case study versus 6 (12.0%) in control case as shown in **Table (1)**.

**Namakin et al.**<sup>10</sup> reported that occurrence of febrile seizures has a predilection towards male. In Talebian et al. 11 study there was no significant differences in the prevalence of febrile seizure regarding sex distributions. And this agrees with our results where male (26) and female (24) **Table (1)**.

Our results contradict with **Yousefichaijan et al.**<sup>12</sup> who showed that the prevalence of anemia in the febrile convulsion group was considerably lower than that of the control group so that 22.5% of the children in the febrile convulsion group suffered from anemia, while 34.0% of the children in the control group were affected with anemia ( $P < 0.001$ ). There were significant differences between the febrile convulsion group and the control group regarding blood indices such as hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) as well, so that all these indices were higher in the febrile convulsion group as compared to the control group.

In the present study; Magnesium (Mg) level decreased significantly in case study when compared with control (Mg;  $1.54 \pm 0.48$  mg/dl versus  $2.05 \pm 0.27$  mg/dl), calcium (Ca) level decreased significantly in case study (Ca;  $8.69 \pm 0.42$  mg/dl versus  $9.14 \pm 1.11$  mg/dl), potassium level (K) decreased significantly in case study ( $4.08 \pm 0.38$  mg/dl versus  $4.39 \pm 0.54$  mg/dl) and associated with insignificant decrease of sodium level (Na ) in case study

( $138.32 \pm 2.58$  mg/dl versus  $138.83 \pm 1.95$  mg/dl), respectively.

Our study compatible with Baek et al. 5 who noticed that Hypomagnesemia and mild hyponatremia were more common in patients with febrile seizure. **Talebian et al.**<sup>11</sup>, revealed that the serum magnesium levels are significantly lower than compared to normal children.

**Namakin et al.**<sup>14</sup> reported that a significantly low serum Mg level was found in patients with febrile convulsion as compared with the controls. Also, **Debroy and Baruah**<sup>15</sup> have reported that the mean serum concentration of Mg was significantly lower in the children with febrile convulsion<sup>16, 17</sup>.

Mg is involved in neuronal functions and inhibits the facilitatory effects of Ca on synaptic transmission. It exerts a voltage dependent blockage of N methyl-D aspartate (NMDA) receptor channel<sup>14</sup>.

In the current study, a significantly low Ca concentration was found in patients with febrile convulsion as compared with the controls and K concentrations were different in the two groups. Ca and K concentrations in the FS

group were lower than in the control group<sup>16</sup>.

**Al-Rubae et al.**<sup>18</sup> showed that low levels of serum calcium and sodium were observed in FSs patients when compared to control group while no significant difference in potassium level between patient and control. In some studies, the electrolyte measurements are done by photometric method and that are less accuracy than electrolytes analyzer because the intervals' reference of electrolytes is very minutes, so it exposed to some errors in photometric method.

Reduced serum Calcium causes increased neural excitability. Low ionized Calcium levels in the extra cellular fluid, by binding to the exterior surface of the Sodium channel protein molecule in the plasma membrane of nerve cells, increasing the permeability of neuronal membranes to sodium ions, causing a progressive depolarization thus increases the possibility of action potentials. When Calcium ions are absent, the voltage level required to open voltage gated Sodium channels is significantly altered (less excitation is required). With hypocalcemia, action potentials may be spontaneously generated causing contraction of peripheral skeletal muscles resulting in clinical seizures<sup>19</sup>.

**Chou et al.**<sup>20</sup> and **Maksikharin and Prommalikit**<sup>21</sup> noted that hyponatremia is common in cases of febrile seizure. Patients with hyponatremic febrile seizure had increased arginine vasopressin levels on the first day of admission, and that they had decreased sodium and osmolality levels on the second day. These findings suggest that fever and other non-osmotic stimuli lead to excess arginine vasopressin, causing transient mild hyponatremia<sup>5</sup>.

In a study of **Bharathi and Chiranjeevi**<sup>9</sup> mild hyponatremia was usually measured immediately after febrile seizure in the emergency room, thus, which is thought to be due to febrile illness or mild dehydration rather than excessive arginine vasopressin secretion. Hypomagnesemia was noted in 86% of patients with simple febrile seizure.

Sodium is the dominant extracellular cation, which determines the fluid movement. Whenever the level of sodium becomes low, it causes excess water to enter the cells. Extracellular hypo-osmolarity causes shift of fluid from intravascular space to intracellular space; most of the cells can expand, except for the neuronal

cells, because brain is confined to a bony calvarium, where expansion is limited. Hence, this results in intracerebral edema which causes constant irritation of the neurons, ultimately resulting in seizures. As the sodium level goes down, seizure is more likely to be recurrent<sup>22, 23</sup>.

The mean serum sodium level was significantly lower in simple febrile seizure (SFS) and complex febrile seizure (CFS) groups than control group and the presence of relative hyponatremia (RH) was observed in 37 (17.78%) children with SFS and 20 (31.7 %) children with CFS. Thus, the low serum sodium level indicated the significant relationship with febrile seizure occurrence<sup>2</sup>.

### **CONCLUSION**

Magnesium level decreased significantly in cases with febrile convulsion when compared with children with fever without convulsion. Calcium, potassium level decreased significantly in children with febrile seizure associated with insignificant decrease of sodium level. There is significant association between hyponatremia, hypocalcemia, and febrile convulsions. It was also concluded that there was no association in children with febrile seizure of various age groups,

gender in relation to serum magnesium levels.

### **RECOMMENDATION**

- Mg supplementation to infants with history of febrile seizures.
- Further research still needed to investigate the status of serum magnesium in children with febrile seizures.
- Estimating the levels of other micronutrients like zinc, selenium, copper, and iron in febrile seizures may throw light on probable etiology.
- Health education for parents about febrile seizures precautionary acts and controls at home through clear induction programs and applications.

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# تقييم نسبة الماغنيسيوم في الدم في حالة التشنجات الحرارية

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**خلفية البحث:** النوبات التشنجية هي أكثر الاضطرابات العصبية شيوعاً بين الأطفال ومعدل الإصابة أعلى في الأطفال الذين تقل أعمارهم عن 3 سنوات، مع انخفاض معدل تواترها في الأطفال الأكبر سناً. إن التشنجات الحرارية هي أكثر أشكال النوبات التشنجية شيوعاً في مرحلة الطفولة. يتراوح معدل انتشار الصرع في البلدان المتقدمة بين اربعة وعشرة افراد لكل ألف فرد في السنة مع معدلات انتشار أعلى بكثير في البلدان النامية.

**الهدف من البحث:** فحص المغنيسيوم لدى الأطفال المصابين بنوبات التشنجات الحرارية مقارنة بالمجموعة الضابطة.

**المرضى وطريق البحث:** تمت هذه الدراسة على 100 طفل. تتراوح أعمارهم بين 6 أشهر و5 سنوات 50 طفلاً يعانون من تشنجات حرارية و50 طفلاً دون تشنجات حرارية.

**نتائج البحث:** في هذه الدراسة، كان العمر قابلاً للمقارنة تقريباً بين الحالات المدروسة؛ (العمر؛  $1.01 \pm 2.45$  سنة في مجموعة الحالات مقابل  $2.54 \pm 1.23$  سنة في المجموعة الضابطة). يوجد 26 طفل (52.0%) ذكور في المجموعة الاولى مقابل 24 طفل (48%) مع وجود فروق ليس لها دلالة إحصائية. كان الوزن والطول قابلين للمقارنة تقريباً بين الحالات المدروسة؛

(الوزن؛  $2.51 \pm 12.3$  كجم في مجموعة الحالات مقابل  $2.87 \pm 12.6$  كجم في مجموعة الضابطة والطول؛  $11.24 \pm 86.5$  سم مقابل  $11.34 \pm 88.98$  سم، على التوالي). ارتفعت درجة الحرارة في مجموعة الحالات ارتفاعاً ذو دلالة إحصائية  $0.16 \pm 39.03$  درجة مئوية بالمقارنة مع المجموعة الضابطة  $0.28 \pm 38.92$  درجة مئوية. في هذه الدراسة، انخفض مستوى المغنيسيوم بشكل ملحوظ في حالات الدراسة بالمقارنة مع مجموعة التحكم ( $1.54 \pm 0.48$  مجم / ديسيلتر مقابل  $2.05 \pm 0.27$  مجم / ديسيلتر) مع وجود فروق ذات دلالة إحصائية. انخفض مستوى الكالسيوم بشكل ضئيل في حالات الدراسة ( $1.2 \pm 8.69$  مجم / ديسيلتر مقابل  $1.11 \pm 9.14$  مجم / ديسيلتر)، انخفض مستوى البوتاسيوم بشكل ضئيل في حالات الدراسة ( $0.38 \pm 4.08$  مجم / ديسيلتر مقابل  $4.39 \pm 0.54$  مجم) والمرتبط بانخفاض طفيف في مستوى الصوديوم في حالات الدراسة ( $2.58 \pm 138.32$  مجم / ديسيلتر مقابل  $1.95 \pm 138.83$  مجم / ديسيلتر)، على التوالي.

**الاستنتاج:** انخفض مستوى المغنيسيوم بشكل ملحوظ في حالات التشنج الحموي عند مقارنته بالأطفال المصابين بالحمى دون تشنج. انخفض مستوى الكالسيوم والبوتاسيوم بشكل ضئيل عند الأطفال المصابين بنوبة حموية مرتبطة بانخفاض غير ملحوظ في مستوى الصوديوم. توجد علاقة معنوية بين نقص صوديوم الدم ونقص كالسيوم الدم والتشنجات الحموية. كما انتهت الدراسة إلى عدم وجود ارتباط بين الأطفال المصابين بالنوبات الحموية من مختلف الفئات العمرية والجنس بالنسبة لمستويات المغنيسيوم في الدم.

**الكلمات الدالة:** المغنيسيوم، النوبات، نوبات الحمى.