EVALUATION OF SERUM IRON AND ZINC LEVELS IN CHILDREN WITH FEBRILE SEIZURES

By


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ABSTRACT

Background: febrile seizures (FS) are the commonest cause of convulsions in children during the first five years of life, many factors can exacerbate the occurrence of febrile seizures.

Objectives: This study was done to evaluate the serum zinc and iron levels in children with febrile seizures.

Patients and methods: this was a prospective case-control study that was including 120 children aged 6-60 months attend to Al-Azhar university hospital Asyut in the period from August 2020 to August 2021, with fever, sixty patient of them has fever with convulsions (case group) and the other sixty patient has fever without convulsions (control group). Both groups fulfill the inclusion and exclusion criteria of the study and subjected to complete history, physical examination, routine investigations and serum iron and zinc levels evaluation.

Results: our study reveals that serum iron and zinc levels are significantly deficient in case group than control group (40.89±21.0), (59.96±17.51) vs (71.60±39.58), (94.22±12.50) respectively with P value (0.000) for both. Also the hematologic indices and serum ferritin were significantly lower in case group than control group.

Conclusions: Serum iron and zinc levels are significantly lower in patients with febrile seizures than febrile patients without seizures.

Keywords: iron, zinc, children, febrile seizures.

INTRODUCTION

Febrile seizures are seizures that are caused by a sudden spike in body temperature with fevers greater than 38°C or 100.4°F, with no other underlying seizure-provoking causes or diseases such as the central nervous system...
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(CNS) infections, electrolyte abnormalities, drug withdrawal, trauma, genetic predisposition or known epilepsy. Febrile seizures categorize as either simple febrile seizures or complex febrile seizures (Xixis K L et al., 2021).

Iron plays an important role in the metabolism of several neurotransmitters. In the case of IDA, the levels of aldehyde oxidase, monoamine oxidase, and the expression of cytochrome C oxidase, a marker of neuronal metabolic activity, are decreased. In developing countries, iron deficiency is the most prevalent nutritional problem, (Vaghela R & Mandot S, 2020) (Srinivasa S and Reddy SP, 2014), especially, among infants aged 6–24 months (Habibian N et al., 2014). Iron deficiency can affect a developing brain by altering the development of hippocampus neurons, impairment of energy metabolism, and alterations in synaptic neurotransmitter systems including norepinephrine, dopamine, glutamate, gamma-aminobutyric acid, and serotonin (Lozoff B, 2011). IDA is common during the 2nd and 3rd years of life and is associated with developmental and behavioral impairments; hence, it can influence motor and cognitive skills (Jáuregui-Lobera I, 2014). As iron plays an important role in the function of various enzymes and neurotransmitters in the CNS, low serum levels of ferritin may lower the seizure threshold (Vaghela R & Mandot S., 2020).

Trace elements have several influences in the CNS. They are involved in Ion channels, synaptogenesis, membrane lipid peroxidation, etc. Over the past years, it was considered that trace elements may play a role in the pathogenesis of febrile seizure. It has been suggested that zinc as an essential trace element plays a role in the pathogenesis of seizures (Heydarian F et al., 2020). There are many studies comparing the serum level of zinc in febrile seizure. In some studies levels of zinc in febrile seizure have been reported to be lower when compared with febrile cases without seizures (Hubaira et al., 2018) but in some studies no significant difference was reported (Maheshwari N et al., 2018).

Aim of the work

The aim of our study was to evaluate the serum zinc and iron levels in children with febrile seizures.

SUBJECTS AND METHODS

This was a case-control study, conducted on one hundred twenty children attending to pediatric department at Al-Azhar university.
hospital Asyut in the period from August 2020 to August 2021. Sixty children aged 6 to 60 months with febrile convulsions were taken as case group. Cases with seizures due to CNS infection, epilepsy, electrolyte disturbances and metabolic disorders were excluded from the study. Sixty children of matched age and sex with fever but without convulsions were included as a control group.

**Ethical considerations:**

The present study was conducted in accordance with international ethical standards and applicable local registry rules. An approval of the study was gained from the academic and ethical committee of Al-Azhar Assiut Faculty of Medicine, Al-Azhar University. All participants’ caregivers received a written consent form. The informed consent was clear and indicated the purpose of the study, and their freedom to participate or withdraw at any time without any obligation. Furthermore, participants’ confidentiality and anonymity were assured by assigning each participant with a code number for the purpose of analysis only. The study was not based on any incentives or rewards for the participants. The study was conducted in accordance with Helsinki standards as revised in 2013.

The author declared that there is no funding and no conflict of interest regarding the study and publication.

Sample size calculation was carried out using G*Power 3 software *(Faul et al., 2007)*. A calculated minimum sample of 120 participants divided into equal groups (60 children with FS and sixty children with fever but without FS) was needed to detect an effect size of 0.3 in the rate of IDA among FS patients, with an error probability of 0.05 and 80% power.

Both groups underwent; full history taking, complete physical examination, and investigations (CBC by hematology cell counter Sysmex X N _ 330, serum ferritin by kinetic fluorescence using TOSOH AIA -360, and serum iron, total iron binding capacity and serum zinc by automated chemistry analyzer Beckman Coulter AU 480). Axillary temperature > 37.7 was recorded as fever *(Aziz K T et al., 2017)*. Iron deficiency anemia was diagnosed by decreased hemoglobin (<10.5g/dl), MCV (<71fl), RBC count (<3.8), hematocrit (<33), MCH (<23 pg), and MCHC (<31 g/d) and increased RDW (>15) *(Miniero R et al., 2019)*.

**Statistical analysis:**
Data was revised, coded, processed and analyzed using IBM-SPSS program (Statistical Package for Social Science) for windows version 20 (SPSS Inc., Chicago, IL, USA). Data were presented as number, percentage, mean, median, and SD using $\chi^2$ test for comparing qualitative variables. Independent samples $t$ test was used to compare quantitative variables. P value was considered significant if $P$ value less than or equal to 0.05 after consulting a statistician.

**RESULTS**

**Table (1): Age, sex, and temperature of the study groups**

<table>
<thead>
<tr>
<th></th>
<th>Case group (n: 60)</th>
<th>Control group (n: 60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (month)</td>
<td>26.18 ±11.9</td>
<td>26.9 ± 12.2</td>
<td>0.881</td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (65%)</td>
<td>42 (70%)</td>
<td>0.724</td>
</tr>
<tr>
<td>Female</td>
<td>21 (35%)</td>
<td>18 (30%)</td>
<td></td>
</tr>
<tr>
<td>Temperature (℃)</td>
<td>39.1 ± 0.4</td>
<td>38.8 ± 0.5</td>
<td>0.781</td>
</tr>
</tbody>
</table>

This table shows no statistical significant difference ($P$-value <0.05) between patients and control as regard demographic data.

**Table (2): Hematologic values of the study groups**

<table>
<thead>
<tr>
<th></th>
<th>Case group (n: 60)</th>
<th>Control group (n: 60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb level (gm/dl)</td>
<td>10.4 ± 1.1</td>
<td>11.8 ± 1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Hematocrit percent</td>
<td>32.17 ± 3.91</td>
<td>35.01 ± 3.83</td>
<td>0.001</td>
</tr>
<tr>
<td>RBCs count</td>
<td>3.89 ± 0.51</td>
<td>4.32 ± 0.72</td>
<td>0.04</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>71.2 ± 1.3</td>
<td>75.9 ± 2.4</td>
<td>0.03</td>
</tr>
<tr>
<td>MCH</td>
<td>23.94 ± 2.6</td>
<td>26.21 ± 3.51</td>
<td>0.01</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.0 ± 0.93</td>
<td>33.1 ± 1.3</td>
<td>0.03</td>
</tr>
<tr>
<td>RDW</td>
<td>13.7 ± 0.6</td>
<td>13.93 ± 0.53</td>
<td>0.07</td>
</tr>
</tbody>
</table>

This table shows highly significant statistical difference ($P$-value <0.001) as regard to RBCs count, MCV, MCH and MCHC, with no statistically significant difference as regard to RDW, between patients and control.
Table (3): Serum iron status and zinc level in the study group

<table>
<thead>
<tr>
<th></th>
<th>Case group (n: 60)</th>
<th>Control group (n: 60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron (µg/dl)</td>
<td>40.89 ± 21.11</td>
<td>71.60 ± 39.58</td>
<td>0.0001</td>
</tr>
<tr>
<td>Serum ferritin (ng/ml)</td>
<td>39.18 ± 18.99</td>
<td>69.82 ± 32.13</td>
<td>0.001</td>
</tr>
<tr>
<td>TIBC</td>
<td>378.27 ± 46.17</td>
<td>325.21 ± 41.33</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum zinc (µg/dl)</td>
<td>59.96 ± 17.51</td>
<td>94.22 ± 12.50</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

This table shows highly significant statistical difference (p-value < 0.001) as regard to Serum iron, Serum ferritin, and serum zinc, and statistically significant difference (p-value <0.05) as regard to TIBC, between patients and control.

**DISCUSSION**

FS is a common neurological problem in children. Etiopathogenesis of FS is not known. Most factors that lead to FS include iron deficiency, family background, genetic factors, immunological disorder, and zinc deficiency (Abdelrahman R A et al., 2020).

Iron has several biological impacts, and it is involved in important neurological processes, such as neurotransmitter metabolism, myelin formation, and brain energy metabolism. According to some experimental studies, in the case of iron deficiency, along with that of gamma aminobutyric acid, iron concentration decreases in some brain regions (hypothalamus, mesencephalon, thalamus, hippocampus, and corpus striatum) (Kartal A T & Mutlu Z C, 2021).

Serum zinc has an important role in good functioning of the central nervous system. Zinc is mainly present in the hippocampus area. Zinc deficiency leads to FS. In patients with FS, the cause of low serum levels of zinc is unknown, although acute infection and fever play an important role. During fever or tissue injury, the release of interleukin and tumor necrosis factor may result in low level of serum zinc (Abdelrahman, R A et al., 2020).

In the present study both the control and case groups were matched regarding to age, sex, and temperature that were important for decreasing the bias in results.

Our study revealed that the hemoglobin (Hb) level, hematocrit (HCT) percent, red blood cells (RBCs) count, mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell
hemoglobin concentration (MCHC), are significantly lower in case group than control group, that was in agreement with the study done by Hameed et al., (2019), Aziz et al., (2017), Kartal, A T & Mutlu Z C (2021), Mahmoud et al., (2021), Khan Z et al., (2021), Khan S A et al., (2021), and Fallah et al., (2013).

In contrast to results of our study, Shamallakh et al., (2021), showed no significant difference between patient and control groups regarding to Hb and MCV, also Yarigarravesh et al., (2021) found no significant difference between patient and control groups regarding to Hb and HCT. Bidabadi E & Mashouf M (2009), revealed that there was no significant difference between patient and control groups regarding to Hb, HCT, MCV, MCH, and MCHC, but found that the hemoglobin level was significantly higher in case group than control group. Also karimi et al., (2019) found no significant difference between patients with febrile seizures and febrile patients without seizures regarding to Hb, HCT, RBCs, MCV, MCH and MCHC levels.

In the present study we found that serum iron and serum ferritin levels were significantly lower in case group than control group and the TIBC was significantly higher in case group than control group, that’s mean that iron deficiency is one of the factors that exaggerate the occurrence of febrile seizures in a genetically susceptible children. These results were correlated with the results of with the results of Hameed et al., (2019), Kartal A T & Mutlu Z C (2021), Khan Z et al., (2021), Khan S A et al., (2021), Jang et al., (2019), Mahmoud et al., (2021), Aziz et al., (2017), Sharif et al., (2016), Habibian et al., (2014) and Fallah et al., (2013), all of them conclude that iron deficiency is more prevalent in patients with febrile seizures than febrile patients without seizures. In contrast to our results Bidabadi E & Mashouf M (2009), Yarigarravesh et al., (2021) and Shamallakh et al., (2021) whom conclude that there is no effect of iron deficiency anemia on the development of febrile convulsions.

The results of our study regarding serum zinc level showed that there is significantly low serum zinc level in patients with febrile seizures as compared to febrile patients without seizures. Zinc plays a vital role in the neuronal terminals of the hippocampus and amygdala by producing pyridoxal phosphate
and affecting glutamatergic, gamma-aminobutyric acidergic (GABAergic), and glycinerergic synapses. Glutamic acid decarboxylase (GAD) acts as a major inhibitory neurotransmitter in the synthesis of gamma-aminobutyric acid (GABA). A study by Ganesh R and Janakiraman L (2008) on 38 children with febrile convulsion and 38 children as a control group, aged between 3 months and 5 years, indicated that a serum zinc deficiency was significantly more prevalent in their case group than in the control group. Another study has reported that there is a correlation between disruption in Zn2+ homeostasis and fever seizure (Nabavi F et al., 2021). The results of our study are congruent with the studies done by Nabavi F et al., (2021), Mahmoud et al., (2021), Abdelrahman R A et al., (2020), Debroy P & Baruah A (2021), Heydarian et al., (2020), Arul et al., (2020), Hameed et al., (2020) and Sowjan et al., (2019), as all of them conclude that there was significant decrease in serum zinc level in children with febrile seizures than those without febrile seizures. On contrary to our results Shamallakh et al., (2021) and Singh V & Yadav D (2018) revealed that serum zinc level has no effect on the frequency of febrile seizures as compared to febrile patients without seizures.

**CONCLUSION AND RECOMMENDATION**

From the finding that was proved in our study we conclude that iron and zinc deficiencies have a role in the development of febrile seizures in genetically susceptible children, hence iron and zinc supplementation can decrease the frequency of febrile seizures. We also recommend further evaluation of the frequency of febrile seizures in iron and zinc deficient children as compared to children with febrile seizures but without iron and zinc deficiency.

**REFERENCES**


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تقييم مستوى الحديد والزنك في بلازما الأطفال الذين يعانون من التشنجات الحرارية

خلفية البحث:

تعد التشنجات الحرارية أسباب حديثاً للتشنجات في الأطفال تحت عمر خمس سنوات، وهنالك العديد من العوامل التي يمكن أن تؤثر على حدوثها.

أهداف البحث:

يهدف هذا البحث إلى تقييم مستوى الحديد والزنك في الأطفال اللذين يعانون من تشنجات حرارية.

المرضى والطرق:

دراسة مستقبيلة تشمل على 120 طفل تتراوح أعمارهم من 6-60 شهر حضروا إلى مستشفى كلية الطب جامعة الأزهر بأسيوط في الفترة من أغسطس 2020 حتى أغسطس 2021، جميعهم يعانون من ارتفاع في درجة حرارة الجسم. ستون طفل منهم يعانون من تشنجات حرارية وقد تم تصنيفهم على أنهم المجموعة المريضة، وستون آخريون يعانون فقط من ارتفاع درجة حرارة الجسم بدون تشنجات حرارية وقد تم تصنيفهم على أنهم المجموعة المجموعة المتحكمة. كما لمهم المجموعتين يتتوفر بهم جميع خصائص الشمول والاستبعاد.
وقد تعرض كلا من المجموعتين لاخذ تاريخ مرضي كامل وفحص جسدي وعمل الفحوصات الروتينية وقياس مستوى الحديد والزنك في الدم.

النتائج:

أوضحت النتائج أن مستوى الحديد والزنك في الدم أقل في المجموعة المريضة عن المجموعة المتحكمية مع وجود دلالات إحصائية واضحة، كما أوضحت النتائج أيضا أن مؤشرات الدم ومستوى مخزون الحديد أقل في المجموعة المريضة عن المجموعة المتحكمة مع وجود دلالات إحصائية واضحة.

الاستنتاج:

يستنتج من الدراسة أن الأطفال المصابة بالتثبيتر الحرارية يعانون أيضا من نقص الحديد والزنك في الدم.

التصويتات:

نوصي باعطاء الأطفال الذين يعانون من حدوث تثبيتر حرارية جرعات محددة من الحديد والزنك للتقليл من معدل حدوث التثبيتر الحرارية. كما نوصي الدراسة أيضا بعمل المزيد من الأبحاث في هذا الشأن.