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Procalcitonin, Calcium, and Magnesium in Patients with Febrile Seizure during One-Hour Attack

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Procalcitonin (PCT) is a marker used as an indicator of severe bacterial infection, which causes febrile seizure (FS). In this study, the level of PCT in patients with FS during the first hour of attack was investigated. Furthermore, the correlation between PCT and serum Ca and Mg was determined.
Methodology: Sixty children (26 male and 34 female) with hyperthermia-induced seizures participated in the study. Blood sampling was performed when seizure attack elapsed (within the first hour of the attack). Patients were classified according to sex, Ca level, C-reactive protein (CRP, positive >6 mg/L), and PCT level (high PCT>0.5ng/mL). Thirty healthy children were selected as the control group.
Results: PCT level increased in patients compared with that of the control group. Patients with normal or hyperPCT showed no correlation between PCT level with the total and ionized Ca and

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Mg. The PCT level between the hypocalcaemic and normocalcaemic groups was not significantly different. The PCT level significantly increased ($p<0.05$) in the group with higher CRP compared with that of the normal CRP group. During the first hour of FS attack, PCT increased with the increase in CRP and no correlation was observed between PCT and the total and ionized serum Ca and Mg levels.

Conclusion: PCT increased and was correlated with CRP in patients with FS during the first hour of attack. The results indicated that PCT elevation is due to the infection and has no evident effect on Ca metabolism in the patients. It can be concluded that the increase in PCT may be due to the FS as a leading cause rather than the bacterial infection.

Keywords: Procalcitonin; febrile seizure; calcium and magnesium.

1. INTRODUCTION

Febrile seizure (FS) is the most common cause of seizures in children with unknown etiology [1]. Procalcitonin (PCT), a pro-peptide of calcitonin produced in the C-cells of the thyroid gland, has been proposed as a marker of severity in various diseases, such as septicemia, pneumonia, and meningitis, as well as fungal and parasitic infections [2]. Several researchers have studied the usefulness of PCT in FS diagnosis and found that the diagnostic efficiency of PCT is higher than that of the C-reactive protein (CRP) in patients with infectious diseases [3,4]. The measurement of PCT is a helpful marker in bacterial infection and sepsis [5,6], because of its diagnostic accuracy and good correlation with the etiology and severity of infection [7]; thus, PCT can be used to differentiate patients with bacterial and nonbacterial infectious causes [8,9], such as fungal infection [10]. However, the correlation between the PCT and Ca levels in patients with FS has not been thoroughly studied.

Serum and urinary Ca levels have been previously studied in children with FS [11,12]. Critical illness is associated with decreased serum total and ionized Ca levels, which are correlated with the severity of the underlying disease [12]. In addition, the total and ionized hypocalcaemia are more observable with the increasing severity of infection and occur in parallel with a marked increase of calcitonin precursors [12]. Previous studies have indicated that serum Mg remains constant in patients with FS compared with that of the control group [13].

In the present study, serum PCT level and its correlation with the serum total and ionized Ca and Mg in patients with FS during the first hour of attack caused by seizure was determined.

2. SUBJECTS AND METHODS

2.1 Subjects

Sixty children (26 male and 34 female) with hyperthermia-induced seizures participated in the study. The included patient's age range was between 10-50 months. The patients were recruited from the Al-Husseini Hospital in Karbala Governorate, Iraq from August 2013 to January 2014. Blood sampling was performed when the seizure attack elapsed (within the first hour of the attack). 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 Iraqi Ministry of Health were followed in the study. The patients were treated with antibiotics, and some patients with positive blood culture (17 out of 60) have responded to the treatment, indicating bacterial infection mostly by *Streptococcus pneumonia*. Any child who did not respond to antibiotics treatment and suspected to have epilepsy, viral, and fungal infections were excluded from the study. The patients were further classified according to Ca level (hypocalcaemia, S.T.Ca<2.1 mmol/L) and PCT level (high PCT> 0.5 ng/mL) [14].

Exclusion Criteria: This study excluded patients with well-known history of epilepsy. This study also excluded the patients who were taking Ca or Mg supplements. Moreover, patients with any evident major systemic diseases, including diabetes mellitus, cardiovascular diseases, or other endocrine disorders, were excluded as well.

Thirty 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.

2.2 Methods

Serum PCT was measured using ready-to-use ELISA kits supplied by DRG® International, Inc., USA. The human PCT ELISA is a sandwich-enzyme immunoassay for measuring human PCT. Serum glucose, total calcium (T.Ca), total magnesium (T.Mg), total serum total protein (STP), and serum albumin were spectrophotometrically determined using ready-to-use kits supplied by Spinreact®, Spain. Serum ionized Ca and Mg levels were calculated using the following formulas:

Ionized Mg = $(0.66 \times T.Mg^{2+}) + 0.039$ [15]
Ionized Ca = $(60.25 \times T.Ca^{2+}(mmol/L)) - (TSP(g/dl) \times 3/8)/(60.5 + (TSP(g/dl))$ [16]

2.3 Biostatistical Analysis

The results of the distribution types of variables were examined via Kolmogorov–Smirnov test. The results of the analysis classified the variables into two types according to the statistical distribution: normally distributed variables and nonparametric variables.

The results were expressed as mean ± standard deviation for normally distributed variables. Pooled 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.

The results were expressed as medians for the nonparametric variables that are not normally distributed. Mann–Whitney U test was used to compare the patients and the control group. Spearman's correlation coefficients (ρ, rho) were determined to estimate the correlation between the parameters. All statistical analysis was performed using SPSS Statistics Program version 21, IBM–USA.

3. RESULTS AND DISCUSSION

3.1 Comparison between Patients with FS and the Control Group

The comparison between the patients and control group is presented in Table 1.

The serum level of I.Ca/Mg, FBS, T.Mg, and I.Mg significantly decreased ($p < 0.05$) in the patients compared with that of the control group. However, PCT level increased in the patients compared with that of the control group.

The increase in the PCT level in patients with FS compared with that of the control group has been discussed in previous study [17]. PCT has been proposed as a marker to identify the presence of systemic infections. Upon admission to the emergency department, the patients had seizures and most children (51 out of 60) had body temperatures higher than 39°C ("fever for investigation"). The body temperature of the other 9 patients were round 38°C. PCT was measured at clinical diagnosis and after 24 and 48 hours; two blood cultures were performed. A positive PCT is a sensible tool with moderate specificity at 48 hours after the clinical diagnosis of neonatal sepsis [18].

In the present study, patients had a FS symptom and not a disease that may be due to different etiologies. Some of our patients had bacterial infection, as shown by positive blood culture and their good response to antibiotics. The most common cause of this bacterial infection may be due to the environmental pollution and hospital-acquired infection in the Holly Karbala city. The probability of the bacterial infection increases in Iraq due to the wars and their consequences on the health and other related services that the governorate cannot supply efficiently to the people. PCT increases in bacterial infection and is an accurate predictor for serious bacterial infection [19,20]. These results are supported by other studies, which showed that PCT levels are significantly higher in children with positive blood cultures than those with negative blood cultures. Elevated PCT levels are predictive of bacteremia [21], and PCT is used as a rapid marker to identify bacteremia [22]. Other research showed that PCT performs better than CRP in identifying infants with bacterial infection; thus, PCT is apparently the optimal marker for ruling out invasive bacterial infection [23,24]. However, other research revealed that PCT level is not correlated with the presence of secondary bacterial infections except in severe cases of sepsis [6]. Table 1 shows the general state of mild hypoglycemia in patients with FS compared with that of the control group. Seizure caused by hypoglycemia represents less than 1% of the patients within the seizure group and is not considered as the major cause [25]. In the present study, the significant difference in glucose level is due to the loss of appetite of the patients with fever as well as the less frequent

feeding time and quantity in ill patients. I.Ca/Mg was significantly different in children with seizure compared with that of the control group, whereas serum total and ionized Ca were not significantly different. These results are in accordance with other studies [26-28]. Furthermore, some authors suggest that serum Mg and CSF Mg levels are not significantly different in patients with FS [13]; while a study has reported that Ca, Mg, and K concentrations in febrile patients is lower than that in the control group [29].

To determine the possible correlations between PCT and cations in patients with FS, we present the correlation coefficients between PCT and each measured parameter in Table 2.

The results showed no significant correlation between the measured parameters and the PCT level in patients with FS. These results indicated the different mechanisms for the increase in PCT level and the changes in these parameters in those patients.

3.2 Comparison between Male and Female Patients

All measured parameters were not significantly different between male and female patients with FS.

3.3 Comparison between Patients with Normal and High PCT

Forty eight (82%) out of 60 patients had hyperPCT (PCT > 0.5 ng/mL). The patients with high PCT had a significantly (p=0.018) higher mean age 47.16±16.23 months than the patients with normal PCT 34.92±12.24 months. Analysis showed no significant correlation between PCT and other parameters in the patients with high PCT level (Table 3).

Seventeen (35%) out of 48 patients with hyperPCT had bacterial infection and responded to antibiotics treatments; the patients were discharged from the hospital within a week. A previous study showed that a high percentage of patients with bacterial infection have hyperPCT [30].

3.4 Comparison between Patients with Normal and Hypocalcaemia

Thirteen out of 60 patients (21.7%) were hypocalcaemic (T.Ca<2.1 mmol/L). No significant difference in PCT between the hypocalcaemic and normocalcemic groups.

Table 1. Comparison between patients and control groups

Parameters	Patients (n=60)	Control (n=30)	Significance (p-value)
Age (Month)	27.73±10.36	29.17±11.51	0.08
T. Protein (g/l)	71.52±8.01	73.08±6.27	0.24
Albumine (g/l)	47.03±3.47	48.07±4.53	0.44
T.Mg (mmol/l)	0.92±0.03	1.01±0.04	<0.01*
I.Mg (mmol/l)	0.64±0.02	0.71±0.03	<0.01*
T.Ca (mmol/l)	2.29±0.48	2.36±0.42	0.92
I.Ca (mmol/l)	0.89±0.28	0.88±0.22	0.79
T.Ca/Mg	2.32±0.60	2.59±0.48	0.23
I.Ca/Mg	1.26±0.40	1.37±0.36	0.02*
RBS (mg/dl)	52.41±8.71	74.73±11.39	<0.01*
Procalcitonin (ng/ml)	8.95	0.47	<0.001*

**: Significant difference (p<0.05)*

Table 2. Correlation between PCT level and other parameters in FS patients

		Age	T.Pr	Alb	T.Mg	I.Mg	T.Ca	I.Ca	T.Ca/Mg	I.Ca/Mg	RBS
PCT	ρ	0.14	0.01	-0.19	0.19	0.19	-0.16	-0.1	-0.19	-0.18	-0.14
	p	0.29	0.95	0.14	0.15	0.15	0.21	0.23	0.15	0.18	0.30

Table 3. Correlation of PCT level with the measured parameters in hyperPCT patients

		Age	T.Pr	Alb	T.Mg	I.Mg	T.Ca	I.Ca	T.Ca/Mg	I.Ca/Mg	RBS
PCT	ρ	0.14	0.01	-0.19	0.19	0.19	-0.14	-0.13	-0.17	-0.15	-0.14
	p	0.28	0.95	0.14	0.15	0.15	0.29	0.34	0.19	0.25	0.31

The PCT level had a significant negative correlation with T.Ca (ρ=−0.48, p=0.01), I.Ca (ρ=−0.44, p=0.02), T.Ca/Mg (ρ=−0.48, p=0.01), and I.Ca/Mg (ρ=−0.44, p=0.02) in hypocalcaemic patients. These results indicate that determining serum Ca and Mg with PCT levels is important in patients with FS. The treatment for the infection caused the elevation in PCT, and the presence of hypocalcaemia and hypomagnesemia should be investigated and treated also.

3.5 Comparison between the Positive and Negative CRP Patient Groups

Eighty four of the patients (80%) were CRP-positive (CRP > 6 mg/L). PCT level significantly increased (p<0.05) in the positive CRP group (PCT=9.58 ng/mL) compared with that of the negative CRP group (PCT=6.27 ng/mL). However, no significant difference in all other measured parameters was observed. The increase in the CRP levels indicates the presence of infection [31]; hence, the infection induces the increase in the PCT, as reported in other studies [32,33].

Many studies reviewed by Becker et al. [34] showed that the measurement of PCT can be used as a marker of severe systemic infection, inflammation, and sepsis. A high PCT commonly occurs in infection but can be elevated also in specific noninfectious conditions. Thus, the test is not a specific indicator of infection or sepsis. Apparently, a patient with febrile septic and documented bacteremia may not necessarily have an elevated serum PCT higher than the limit of functional sensitivity of the assay.

The diagnostic accuracy of PCT is similar to those of the CRP infection cases. PCT seems to be a promising marker of infections [7,35]. PCT performs better than leukocyte count and CRP for detecting serious bacterial infection among children with fever from an unknown source. Considering the poor pooled-positive likelihood ratio and acceptable pooled-negative likelihood ratio, PCT is more efficient for ruling out serious bacterial infection than for ruling it in. Existing studies did not define the significance of combining PCT with other clinical information [36,37].

3.6 Comparison between FS Patients with Positive and Negative Blood Culture

Seventeen out of 60 patients (28.3%) were having positive blood culture. The comparison between the patients with negative and positive blood culture results showed that there is significant differences (p<0.05) between positive and negative blood culture groups in the level of PCT (6.74 ng/ml*vs.* 0.64 ng/ml), RBS (48.45 mg/dl*vs.* 63.54 mg/dl), respectively. Higher PCT level in patients with positive blood culture was noticed in recent work [38]. To compare the diagnostic values of either CRP for the diagnosis of infection, CRP gives a sensitivity of 76.9%, specificity of 93.3%, positive predictive value (PV+) of 71.43%, and negative predictive value (PV-) 94.9%. While PCT, at cutoff >0.5 ng/ml, gives a sensitivity of 92.3%, specificity of 91.7%, positive predictive value (PPV) of 70.6%, and negative predictive value (NPV) of 98.2%. These results indicated that the serum PCT has a good diagnostic value for the diagnosis of infection in FS patients comparing with the CRP. The patients who have positive CRP and high PCT level constitute 98% of the FS patients with positive blood culture. These findings are consistent with other previous studies that involved a larger sample size [39,40].

The fact that 28.3% of patients had positive blood culture and 82% had hyperPCT leads to a conclusion that the increase in PCT may be due to the FS as a leading cause rather than the bacterial infection. The mechanism about the association between FS and hyperPCT is not easy to explain due to two important reasons. First, the PCT effect on nervous system is yet to be cleared as seizure is a complex neurological disorder [41]. Second, most researches attributed the increase in PCT in FS to the consequences of bacterial infection and not due to the FS as a syndrome [10,38].

3.7 Comparison between Normo-glycemic and Hypoglycemic Patients with FS

Only two patients from the studied group were hypoglycemic; hence, classifying these patients into two groups may be impractical.

4. CONCLUSION

PCT increased and was correlated with CRP in patients with FS during the first hour of attack. PCT was not correlated with the serum total and ionized Ca and Mg levels. The overall results reveal that PCT elevation has no evident effect on the Ca metabolism of the patients. Therefore, the elevation in PCT is a marker of infection

rather than the effect or for the Ca level in patients with FS.

The main limitations of the present study are the small size of the study groups and lack of the comparison between the serum PCT level at the first hour of attack and after complete cure. This comparison would produce a clear conclusion about the impact of FS on PCT level and *vice versa.*

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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