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ORIGINAL ARTICLE

Postictal Assessment of Serum Copeptin Level in Children with Convulsion

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ABSTRACT

Background: The most prevalent form of childhood seizure disease is febrile convulsion. Measuring copeptin has been demonstrated to be helpful in a number of therapeutic indications for numerous diseases. This study aimed to assess the diagnostic role of serum copeptin in discriminating febrile convulsions from convulsions without fever.

Methods: This case-control study was carried out in the Paediatric Department at Zagazig University Hospital and Kafr Sakr General Hospital. A total of 51 patients were recruited and were divided into three groups: febrile convulsions group (A) included 17 patients, convulsions without fever group (B) included 17 patients and fever only (group C) included 17 patients**.** All the children were subjected to history taking, clinical examination and laboratory investigations, including hematocrit, white blood count with differential, serum sodium, serum glucose, serum calcium level, C-reactive protein (CRP) and Serum copeptin**.**

Results: There was no significant difference between groups regarding age and sex, but there was a significant difference between the three studied groups as regards BMI (kg/m^2) (17.55 ± 2.14 vs 16.88 ± 3.84 vs 14.92 ± 2.67, p = 0.03). There was no significant difference in copeptin levels between the 3 groups (p-value>0.05). There was a non-significant difference with a negative correlation between group C as regards copeptin with CRP (p > 0.05). **Conclusion:** Circulating copeptin has no diagnostic role in discriminating febrile convulsions from convulsions without fever.

Keywords: Febrile convulsion, Copeptin, Children

INTRODUCTION

The most prevalent type of seizure disorder in children is called febrile convulsion. This kind of seizure condition is age-specific, accompanied by a temperature of 38.0 degrees Celsius or above, and does not exhibit any clear symptoms of a specific underlying illness, such as a central nervous system infection or metabolic imbalance **[1]**.

The majority of febrile convulsions are harmless and will go away on their own; hence, treatment is typically not recommended **[2]**.

A febrile convulsion is a type of seizure that can occur in children between the ages of 6 months and 5 years old when they are experiencing an episode of fever. This type of seizure affects 2% to 5% of children and can occur more than once in 30% of cases **[3].**

It has been demonstrated that the pituitary gland hormone arginine-vasopressin (AVP), which is secreted into the bloodstream, plays a role in the thermoregulatory response to convulsions and fever **[4].**

One of the most important hormones in the human body is arginine vasopressin or AVP. Although AVP plays a clinically significant role in regulating fluid balance and vascular tone, accurate determination of mature AVP is challenging and prone to pre-analytical mistakes **[5].**

Recent research has shown that the glycopeptide copeptin, which is composed of 39 amino acids and forms the C-terminal component of the AVP precursor (CT-proAVP), can serve as a reliable and delicate substitute marker for AVP release. Copeptin measurement has been shown to be useful

for several clinical purposes, such as monitoring sepsis and cardiovascular problems and diagnosing diabetes insipidus **[1].** The aim of this study was to assess the diagnostic role of serum copeptin in discriminating febrile convulsions from convulsions without fever.

METHODS

After protocol approval by our Local Ethics Committee (IRB # 6493-13-12-2022), This case-control study was carried out in the Pediatric Department at Zagazig University Hospital and Kafr Sakr General Hospital during the period from March 2022 to August 2023. A total of 51 patients were recruited and divided into three groups, each group of 17 patients: Group A: febrile convulsions group, Group B: convulsions without fever group and Group C: fever only. Parental written informed consent was obtained from parents or guardians of study patients. The work has been carried out by The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The inclusion criteria were age between 6 months and 5 years, medical indication for blood sampling at the emergency department (ED), parental consent to participate in the study, and children with febrile convulsion, fever without convulsion, or convulsion without fever. Excluded criteria were patients aged less than 6 months or more than 6 years, children with neurological episodes, or handicaps.

Every participant underwent history taking and a thorough clinical examination including general and local examination. Galsco coma scale, body mass index (body weight), body temperature and vital signs at the ED, clinical characteristics of the febrile infection. Laboratory investigations included base analyses (hematocrit, white blood count with differential, serum sodium, serum glucose, serum calcium level, and determination of C-reactive protein (CRP). Serum copeptin by ELIZA.

C-reactive protein (CRP): Quantitative determination was performed using turbidimetry on Cobas 6000 (c501). The serum copeptin concentrations were measured using an enzyme-linked immunosorbent assay and quantified using the ELISA technique. DL-CPP-Hu Company provided the kit.

STATISTICAL ANALYSIS

Once data was loaded into the computer, the IBM SPSS software program version 20.0 was used for analysis (Armonk, NY: IBM Corp.). The qualitative data was described using percentages and numbers. The Shapiro-Wilk test was run to verify the distribution's normality. Quantitative data were described using the terms range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). At the 5% threshold, the outcomes were considered significant.

RESULTS

Table 1 showed that children with febrile convulsion did not show any differences from those without fever patients and febrile controls in terms of sex and age ($p > 0.05$). This table shows that there was a significant difference between the three studied groups as regards BMI (kg/m2) (17.55 ± 2.14 vs 16.88 ± 3.84 vs 14.92 ± 2.67, $p = 0.03$). This table shows that there was an insignificant difference between the three studied groups in terms of family history (febrile convulsions, epilepsy or neurological conditions) ($p > 0.05$).

Table 2 showed that the three studied groups had an insignificant difference in copeptin level ($p > 0.05$).

Table 3 showed an insignificant difference between the three studied groups regarding CRP, HCT, and RBS ($p > 0.05$).

Table 4 showed that copeptin had insignificant validity in discriminating Group A (Febrile convulsion) from Group B (Convulsion without fever) as regards the Diagnostic performance ($p > 0.05$)

Table 5 showed that Copeptin had insignificant validity in discriminating Group A (Febrile convulsion) from Group C (Fever only) as regards the Diagnostic performance ($p > 0.05$)

Table 6 showed that copeptin had insignificant validity in discriminating Group B (Convulsion without fever) from Group C (Fever only) as regards Diagnostic performance ($p > 0.05$).

Table 1: Comparison between the three studied groups according to demographic data N= 17

	Group A		Group B		Group C		Test of Sig.	p
	No.	%	No.	%	No.	%		
Gender **Male** **Female**	7 10	41.2 58.8	9 8	52.9 47.1	6 11	35.3 64.7	x^2= 1.119	0.571

	Group A		Group B		Group C		Test of Sig.	p
Age (/years) **Min. - Max.** **Mean ± SD.** **Median (IQR)**	0.58 - 4.20 2.46 ± 1.33 2.0 (1.5 - 4.0)		0.50 - 6.0 2.68 ± 1.96 2.0 (0.75 - 5.0)		0.58 - 5.70 2.79 ± 1.42 3.0 (1.80 - 3.5)		F= 0.184	0.833
Weight (kg) **Min. - Max.** **Mean ± SD.** **Median (IQR)**	6.80 - 17.20 12.23 ± 3.03 12.30 (10 - 14.8)		5.0 - 18.0 11.44 ± 4.0 11.80 (8.7 - 14.0)		8.0 - 17.0 12.30 ± 2.68 12.0 (10 - 14)		0.358	0.701
Height (cm) **Min. - Max.** **Mean ± SD.** **Median (IQR)**	60.0 - 105.0 83.41 ± 13.05 81.0 (75 - 94)		59.0 - 154.0 83.41 ± 23.01 84.0 (68 - 90)		67.0 - 157.0 92.41 ± 20.37 94.0 (76 - 97)		1.236	0.300
BMI (kg/m^2) **Min. - Max.** **Mean ± SD.** **Median (IQR)**	15.15 - 22.78 17.55 ± 2.14 16.91(16.0 -18.3)		7.59 - 25.85 16.88 ± 3.84 16.89(15.6 -18.3)		6.90 - 19.84 14.92 ± 2.67 15.0 (14.6 - 15.7)		3.604*	0.035*
Sig. bet. groups.	p1=0.790,p2=0.034*,p3=0.142							
Family history							**X^2**	**^{MC}p**
Family history **No** **Yes**	14 3	82.4 17.6	14 3	82.4 17.6	16 1	94.1 5.9	1.403	0.674

[IQR: Inter quartile range; SD: Standard deviation; F: F for One-way ANOVA; Test %^{2}: Chi-square test; X2: Chi-square test, and MC: Monte Carlo test]
p: p-value for comparing between the three studied groups
p: p-value for comparing between the three studied groups
p1: p-value for comparing between Group A and Group B
p2: p-value for comparing between Group A and Group C
p3: p-value for comparing between Group B and Group C
*: Statistically significant at $p < 0.05$

Table 2: Comparison between the three studied groups according to Copeptin

	Group A (n = 17)	Group B (n = 17)	Group C (n = 17)	H	p
Copeptin (ng/ml) **Min. - Max.** **Mean ± SD.** **Median (IQR)**	2.65 - 23.76 10.06 ± 6.90 7.37(5.54 -9.99)	2.76 - 24.69 11.44 ± 7.72 10.0 (3.9 - 18.1)	1.99 - 15.93 6.80 ± 3.79 6.54 (3.76 - 8.1)	2.717	0.257

[IQR: Inter quartile range; SD: Standard deviation; H: H for Kruskal Wallis test]
p: p-value for comparing the three studied groups.

Table 3: Correlation between Copeptin and laboratory investigation among the studied groups (n = 51)

Variable	Copeptin (ng/ml)	
	rs	p
CRP	0.022	0.881
HCT	-0.119	0.406
RBCs	0.144	0.314
Na	-0.184	0.196
Ca	**-0.454**	**0.001***

[rs: Spearman coefficient; *: Statistically significant at p ≤ 0.05; HCT: hematocrit; CRP:C-Reactive Protein**]**

Table 4: Diagnostic performance for Copeptin to discriminate Group A (Febrile convulsion) (n = 17) from Group B (Convulsion without fever) (n = 17)

	AUC	p	95% C. I	Cut off#	Sensitivity	Specificity	PPV	NPV	Accuracy
Copeptin (ng/ml)	0.519	0.850	0.311 – 0.727	>9.99	58.82 %	76.47 %	71.4 %	65%	67.6%

[AUC: Area Under a Curve, CI: Confidence Intervals, NPV: Negative predictive value, PPV: Positive predictive value. #Cut off was chosen according to the Youden index]

Table 5: Diagnostic performance for Copeptin to discriminate Group A (Febrile convulsion) (n = 17) from Group C (Fever only) (n = 17)

	AUC	**p**	**95% C.I**	**Cut off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
Copeptin (ng/ml)	0.612	0.263	0.420 – 0.805	<4.05	35.29 %	94.12 %	85.7 %	59.3 %	64.7%

[AUC: Area Under a Curve; CI: Confidence Intervals; NPV: Negative predictive value; PPV: Positive predictive value]

Table 6: Diagnostic performance for Copeptin to discriminate Group B (Convulsion without fever) (n = 17) from Group C (Fever only) (n = 17)

	AUC	**p**	**95% C.I**	**Cut off#**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
Copeptin (ng/ml)	0.668	0.095	0.476 – 0.859	<9.37	88.24 %	58.82 %	68.2 %	83.3 %	73.5%

[AUC: Area Under a Curve; CI: Confidence Intervals; NPV: Negative predictive value; PPV: Positive predictive value]

DISCUSSION

This study showed that Children with Febrile convulsion did not differ from Convulsion without fever patients and febrile controls in terms of sex and age (p > 0.05).

Evers et al. [6] examined the effects of febrile and epileptic seizures on serum neurofilament light chain (sNfL), serum copeptin, and prolactin levels in children with febrile illnesses but no convulsions. The children ranged in age from 6 to 163 months, and 44% of them were female. Age, body weight,

and temperature at home and in the emergency room did not significantly differ between the controls and the febrile seizures (FS) group. Overall, compared to the other groups, the epileptic seizures (ES) group's values for age and body weight were marginally but not significantly higher.

Abd El-Moneim et al. [7] conducted a case-control study to investigate the relationship between copeptin and idiopathic convulsions and the possible use of copeptin as a febrile convulsion biomarker. A comparative study of the analyzed groups' demographics revealed no statistically significant correlations between the kind of convulsions and age ($p = 0.11$), gender ($p = 0.89$), or both.

In agreement with our study, Hussain et al. [8], Soheili et al. [9], Potdar et al. [10] and Heydarian et al. [11] discovered that the age and sex differences between the control group and the group with febrile convulsions were negligible.

This study demonstrated notable variations among the three groups under investigation with respect to BMI (kg/m^2); it was higher in group A (febrile convulsions) (17.55 ± 2.14 vs 16.88 ± 3.84 vs 14.92 ± 2.67, $p = 0.03$).

Evers et al. [6] found no discernible difference in body weight or temperature at home or in the emergency department between the controls and the febrile seizures (FS) group. The epileptic seizures (ES) group did, however, have slightly, but not substantially, higher average body weight values than the other groups.

This study reported an insignificant difference between the three studied groups as regards copeptin level ($p > 0.05$). In agreement, Stocklin et al. [12] discovered that there was no discernible difference in copeptin levels between idiopathic epilepsy and febrile convulsions. Also, Abd El-Moneim et al. [7] showed that there was no statistically significant difference in the copeptin level between fever with convulsions, fever without convulsions, and idiopathic epilepsy.

Contrary to the current results, Stocklin et al. [12] discovered that, in comparison to febrile controls, children experiencing convulsions had noticeably greater amounts of copeptin in their blood. Salam et al. [13] discovered in another investigation that patients with febrile convulsions had considerably greater copeptin levels.

This study showed an insignificant difference between the three studied groups regarding CRP, HCT, and RBS ($p > 0.05$).

In agreement with the current study, Bakhtiari et al. [14] reported an insignificant correlation between CBC, CRP, and copeptin levels. Also, Stocklin et al. [12] found no statistically significant correlation between Copeptin and CRP among the studied groups.

This study demonstrated that there was an insignificant difference between copeptin in discriminating Group A (Febrile convulsion) and Group B (Convulsion without fever) in terms of diagnostic performance ($p > 0.05$). There was an insignificant difference between copeptin to discriminate Group A (Febrile convulsion) from Group C (Fever only) as regards the Diagnostic performance ($p > 0.05$). There was an insignificant difference between copeptin in discriminating Group B (Convulsion without fever) and Group C (Fever only) in terms of diagnostic performance ($p > 0.05$).

Evers et al. [6] showed that the capacity to diagnose seizures varied greatly among the different biomarkers, with copeptin having the greatest AUC levels in comparison to prolactin and sNfL, according to receiver operating characteristic curve analysis.

Abd El-Moneim et al. [7] the results of the ROC analysis showed that serum Copeptin was a significant discriminator between fever with convulsions and fever without convulsions (AUC = 0.702; $p = 0.007$) as well as between fever with convulsions and idiopathic epilepsy (AUC = 0.703; $p = 0.004$). They demonstrated that when used to distinguish between fever with convulsions and fever without convulsions, serum Copeptin had a 90% sensitivity and a 60% specificity according to the ROC analysis.

According to ROC curve analysis, in comparison to our study, Stocklin et al. [12] found that copeptin had a better overall ability than prolactin to distinguish between children with FS and controls. Copeptin also performed better as a diagnostic tool than prolactin.

LIMITATIONS

There were some limitations in this study. This case-control study was conducted at a single centre with a small period for follow-up, so we recommended future larger sample sizes and multicenter studies may explain more about the role of copeptin in the diagnosis of febrile convulsions and discriminate it from other causes of seizures.

CONCLUSION

In conclusion, circulating copeptin has no diagnostic role in discriminating febrile convulsions from convulsions without fever.

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