ORIGINAL ARTICLE

Copeptin as a Serum Biomarker for Febrile Convulsions

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ABSTRACT

Keywords: Copeptin, Serum Biomarker, Febrile Convulsions

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Background: Febrile convulsions are the most common neurologic disorder in the pediatric age group, affecting 2–5% of children between 6 months and 5 years of age. **Objective:** We conducted the present acase control study in order to investigate whether copeptin can be considered as a biomarker for febrile convulsions and its relation with idiopathic convulsions. **Patients and methods:** The present study included 105 children with either febrile convulsions, fever or had epilepsy who were recruited from Pediatric department at Aswan University Hospital. **Results:** There was statistically significant increase in copeptin level in febrile convulsions compared to fever without convulsions and idiopathic epilepsy. There was statistically significant increase in temperature in febrile convulsions than other groups and in fever without convulsions than idiopathic epilepsy. There was statistically significant decrease in hemoglobin ($p < 0.001$), MCV ($p < 0.001$), HCT ($p < 0.001$), in febrile convulsions compared with other groups. There was statistically significant decrease in serum Na in febrile convulsions and idiopathic epilepsy compared to fever without convulsion. **Conclusion**: The present study showed that serum copeptin was a significant discriminator of febrile convulsion from idiopathic epilepsy and fever without convulsions.

INTRODUCTION

Febrile Convulsions are seizures that are caused by a sudden spike in body temperature with fevers greater than 38C or 100.4F, with no other underlying seizure-provoking causes or diseases such as central nervous system infections, electrolyte abnormalities, drug withdrawal, trauma, genetic predisposition or known epilepsy, febrile convulsions categorize as either simple febrile convulsions or complex febrile convulsions [(1)].

In most children, febrile convulsions are related to common infections, e.g., acute otitis media, bronchitis, gastrointestinal or urinary tract infection both of bacterial and viral origin, only rarely are febrile convulsions a symptom of a central nervous system infection (e. g., meningitis), however, a site of infection needs to be confirmed or excluded during the initial diagnostic work-up so as to adjust further treatment [(2)].

The exact aetiology of febrile convulsions is unknown, but it is considered to be the result of a complex interplay between environmental and genetic factors, fever in febrile convulsions is extra-cranial in origin and the high temperature associated with it is a normal physiological response to infection, mechanisms that could explain the process of such convulsions include the

release of cytokines during fever, which cause temporary abnormal electrical activity in the brain [(3)]. Copeptin (COP), the C-terminal fragment of pro-vasopressin was reported to have prognostic value in various diseases including acute coronary syndromes [(4)], cerebral hemorrhage [(5)], congestive heart failure [(6)], pulmonary diseases or sepsis [(7)].

Copeptin is a more stable molecule in plasma and is eliminated partially by renal excretion, therefore it can be used as a surrogate marker of arginine vasopressin, an over activation of the arginine vasopressin system, measured as elevated copeptin levels in plasma, has been linked to cardio-metabolic risk factors [(8)]. Increased serum copeptin levels have been also reported after short hypoxic events**,** which are not uncommon during convulsive episodes[(9)].

Central cyanosis is one of the most frequently reported signs by parents and caregivers of children with febrile seizure, an acute drop in blood pressure during the paroxysmal episode might also trigger copeptin release, in a way similar to that proposed for copeptin increase in elderly patients with syncope [(10)].

The aim of this study was to investigate whether copeptin considered as early sensitive or specific biomarker for febrile convulsions. To findout if copeptin has relation to febrile convulsions subtypes (Simple, complex) or not.

PATIENTS AND METHODS

The study is acase control study. It was conducted on 105 child with age range from (6months – 6years) from Pediatric department in Aswan University Hospital.

Inclusion criteria: children ages from 6 month to 6 years presenting with febrile convulsions, fever, children known to had epilepsy.

Exclusion criteria: children <6 months and >6 years, diabetic patients, children with chronic renal diseases, heart diseases, endocrinal disease, children with C.N.S infection, seizures due to hypoxic ischemic encephalopathy and inborn error of metabolism.

The study population was classified as follow:

Group I (Febrile convulsions cases group):

include 35 children with either simple or complex febrile convulsions.

Group II (idiopathic epilepsy cases group):

Included 35 children diagnosed with epilepsy and presenting with convulsions with the following criteria: known or presumed genetic defect(s) that is not causative of a brain structural or metabolic disorder other than the epilepsy and does not had neither fever nor infection.

Group III (fever without convulsions control group):

35 children presenting with febrile infection without previous history of febrile or afebrile seizure.

Patient in the study was subjected to the following:

1. Full history taking.
2. Full clinical examination including detailed neurological assessment.
3. Laboratory investigations:

   (a) Routine investigations: CBC, serum electrolytes (Na, K, Ca), ABG, lactate and CRP.

   (b) Specific investigations: Post ictal Serum copeptin level during 60 min after convulsion and serum copeptin level during fever.

Serum copeptin assay: Quantitative determination of serum copeptin concentrations was done by sandwich ELISA technique.

Principle of the Assay: This assay employs the quantitative level of Human copeptin in the sample, adopt purified copeptin antibody to coat microtiter plate. Make solid- phase antibody,then add copeptin to wells, combined copeptin antibody with labeled HRP to form antibody-antiboy-enzyme-antibody complex,after washing completely add TMB substrate solution, TMB substrate becomes blue color at HRP enzyme-catalyzed ,reaction is terminated by addition a stop

solution and the color change is measured at a wavelength of 450 nm.the reaction of copeptin in the samples is then determined by comparing the O.D of the sample to the standard curve.

Ethical consideration:

An informed written consent was obtained from all parent‘s caregiver studied groups before getting them involved in the study. The steps of the study, the aim of the study, the potential benefit and hazards, all were discussed with the parent‘s studied groups. Confidentiality of all data was ensured. The parent‘s studied groups have the right to withdraw from the study at any time without giving any reason.

Statistical analysis:

Descriptive statistics: Means, standard deviations, medians, ranges and percentages were calculated. Test of significances: Chi square test was used to compare the difference in distribution of frequencies among different groups. For continuous variables with more than two categories, ANOVA test was calculated to test the mean differences of the data that follow normal distribution, post-hoc test was calculated using Bonferroni corrections for pairwise comparisons. Mann-Whitney U-test was carried out to compare the medians of dichotomous data that don‘t follow normal distribution. ROC curve was depicted to investigate the diagnostic performance of Copeptin as biomarkers for diagnosis of febrile convulsions, analysed as area under the curve (AUC), standard error (SE) and 95% CI. Validity statistics (sensitivity, specificity, positive and negative predictive value –PPV & NPV-) were calculated. A significant p value was considered when it is equal or less than 0.05.

RESULTS

Demographic comparative analysis between the studied groups showed that there were no statistically significant associations between type of convulsions and age (p =0.11) and gender (p =0.89). In contrary, there was statistically significant associations between febrile convulsions and weight (p <0.001); patients with febrile convulsions had significantly lower weight than patients with fever without convulsions and idiopathic epilepsy. In addition, there was statistically significant increase in temperature in febrile convulsions than other groups and in fever without convulsion than idiopathic epilepsy (Table 1).

There was statistically significant decrease in hemoglobin(p <0.001), MCV (p<0.001), hematocrite (p <0.001),and statistically significant increase in platelet(p= 0.026) in febrile convulsions compared with other groups also statistically significant increase in platelet (p= 0.026) in febrile convulsions compared with other groups.

There was statistically significant increase total leucocytic count (p =0.049) in febrile convulsions than fever without convulsions while statistically significant decrease in serum Na (P1= 0.023) ,(P3= 0.003) in febrile convulsions and idiopathic compared to fever without convulsions. In contrary, there was no difference between the study groups in serum K (p =0.708) and serum Ca level (p =0.99).

There was statistically significant increase in CRP (P2= 0.049) in febrile convulsions compared to idiopathic epilepsy while there was statistically significant decrease in CRP (P3=0.002) in idiopathic epilepsy than fever without convulsions .There was statistically significant decrease in HCO3 (P2= 0.011) in febrile convulsions compared to idiopathic epilepsy while statistically significant increase(P3=0.049) in it in idiopathic than in fever without convulsions,

There was statistically significant increase in copeptin level in febrile convulsions (p< 0.001)compared to fever without convulsions and idiopathic epilepsy while there was no difference in PH and lactate between groups (Table 5).

The ROC analysis showed that serum Copeptin was a significant discriminator between febrile convulsions and fever without convulsions (AUC =0.702; p =0.007) and between febrile convulsions and idiopathic epilepsy (AUC =0.703; p =0.004) (Table 2).

The ROC analysis showed that serum Copeptin yielded a sensitivity of 90% and specificity of 60% for discrimination between

febrile convulsions and fever without convulsions. In addition, serum Copeptin yielded a sensitivity of 86% and specificity of 54% for discrimination between febrile convulsions and idiopathic epilepsy (Table 3).

Show copeptin had no significant difference between simple and complex FC (Table 4).

Table (1): Demographic Comparative Analysis between the studied groups.

	Fever without Convulsions (n=35)	**Febrile Convulsions (n=35)**	**Idiopathic epilepsy (n=35)**	**P-value**
Age (years) **P-value****	3.99 ± 1.6 P1=0.072	3.46 ± 0.7 P2=0.067	4.01 ± 1.1 P3= 0.967	=0.111*
Sex: **Male** **Female**	19 (54.3%) 16 (45.7%)	18 (51.4%) 17 (48.6%)	17 (48.6%) 18 (51.4%)	=0.892***
Weight (kg) **P-value****	14.71 ± 2.4 **P1=0.001**	13.01 ± 1.5 **P2<0.001**	15.30 ± 1.9 P3= 0.232	**<0.001***
Temperature (°C) **P-value****	38.59 ± 0.6 **P1 < 0.001**	39.40 ± 0.5 **P2 < 0.001**	37.07 ± 0.7 **P3 < 0.001**	**< 0.001***

*** ANOVA test was used to compare the mean difference between groups.**
****Post-hoc test with Bonferroni corrections was used for pairwise comparisons.**
*****Chi-square test was used to compare the proportion difference between groups.**
--P1= Fever without vs. Febrile, P2=Febrile vs. Idiopathic and P3= Fever without vs. Idiopathic.

Table (2): Diagnostic performance of Copeptin as a biomarker for diagnosis of febrile convulsions, analysed as area under the curve (95% CI).

	AUC*	**95% CI+**	**SE****	**P-value*****
Febrile Convulsions vs Fever without Convulsions	**0.702**	**0.580 - 0.824**	**0.062**	**= 0.007**
Febrile vs Idiopathic epilepsy	**0.703**	**0.581 - 0.825**	**0.062**	**= 0.004**
Idiopathic epilepsy vs Fever without Convulsions	**0.566**	**0.424 - 0.728**	**0.073**	= 0.341

***AUC = Area under the Curve**
****SE = Standard Error+CI = Confidence Interval**
*****Null hypothesis: true area = 0.5**

Table (3): Diagnostic criteria of Copeptin as a biomarker for diagnosis of FC**.**

	Diagnostic criteria		
	F. Convulsions vs Fever without Convulsions	**Febrile vs Idiopathic epilepsy**	**Idiopathic E. vs Fever without Convulsions**
• **AUC**	**0.702**	**0.703**	**0.566**
• **Cut-off**	**1.3**	**1.3**	**1.3**
• **Accuracy**	**75%**	**70%**	**61%**
• **Sensitivity %**	**90%**	**86%**	**67%**
• **Specificity %**	**60%**	**54%**	**55%**
• **PPV %**	**70%**	**65.2%**	**60%**
• **NPV %**	**86%**	**79.4%**	**62.5%**

***Sensitivity (true positives/all diseased); specificity (true negatives/all non-diseased); PPV (true positives/all test positives); NPV (true negatives/all test negatives).**

Table (4): Comparison of Copeptin Level between Convulsions Subtypes (simple, complex).

	Simple Convulsions (n=28)	**Complex (n=7)**	**P-value***
Copeptin Level			
• **Mean ± SD**	2.78 ± 1.9	1.66 ± 0.5	= 0.146
• **Median (Range)**	1.97 (0.8 – 7.9)	1.51 (1.15 – 2.39)	

***Mann-Whitney U-test was used to compare the median differences.**

Table (5): Comparisons of Laboratory Data between the studied Groups

	Fever without Convulsions (n=35)	**Febrile Convulsions (n=35)**	**Idiopathic Epilepsy (n=35)**	**P-value**
Hgb (mg/dl)	12.16 ± 1.2	9.77 ± 1.4	12.01 ± 1.1	**< 0.001***
P-value**	**P1<0.001**	**P2<0.001**	P3= 0.598	
MCV	80.87 ± 3.5	72.41 ± 5.1	79.00 ± 3.9	**<0.001***
P-value**	**P1<0.001**	**P2<0.001**	P3= 0.067	
HCT	34.41 ± 3.6	26.74 ± 4.1	34.69 ± 3.5	**<0.001***
P-value**	**P1<0.001**	**P2<0.001**	P3= 0.757	
Platelet Count	254.91 ± 73.9	293.57 ± 36.6	247.00 ± 54.5	**= 0.026***
P-value**	**P1= 0.035**	**P2= 0.012**	P3= 0.663	
TLC	6.80 ± 1.6	7.75 ± 1.2	7.47 ± 1.3	**=0.049***
P-value**	**P1= 0.017**	P2= 0.439	P3= 0.091	
Na Level	139.43 ± 2.9	138.11 ± 2.4	137.71 ± 1.9	**=0.009***
P-value**	**P1= 0.023**	P2= 0.484	**P3= 0.003**	
K Level	4.20 ± 0.4	4.12 ± 0.4	4.13 ± 0.4	=0.708*
P-value**	P1= 0.464	P2= 0.987	P3= 0.482	
iCa Level	1.21 ± 0.06	1.21 ± 0.07	1.21 ± 0.06	=0.990*
P-value**	P1= 0.898	P2= 0.985	P3= 0.912	
CRP	7.78 ± 1.0	6.37 ± 0.9	4.16 ± 0.2	**= 0.006***
P-value**	P1= 0.208	**P2= 0.049**	**P3= 0.002**	
Lactate Level	1.40 ± 0.4	1.34 ± 0.4	1.31 ± 0.3	= 0.573*
P-value**	P1= 0.510	P2= 0.701	P3= 0.289	
PH Level	7.37 ± 0.02	7.38 ± 0.03	7.37 ± 0.02	= 0.616*
P-value**	P1= 0.511	P2= 0.337	P3= 0.761	
HCO_3 Level	21.83 ± 1.1	21.66 ± 1.2	22.37 ± 1.2	**= 0.030***
P-value**	P1= 0.537	**P2= 0.011**	**P3= 0.049**	
Copeptin Level	1.35 ± 0.2	2.56 ± 0.3	1.56 ± 0.1	**< 0.001***
P-value**	**P1< 0.001**	**P2= 0.001**	P3= 0.448	

*** ANOVA test was used to compare the mean difference between groups**

****Post-hoc test with Bonferroni corrections was used for pairwise comparisons**

--P1= Fever without vs. Febrile, P2=Febrile vs. Idiopathic and P3= Fever without vs. Idiopathic

DISCUSSION

In the present study, we found that the mean age of the included children with febrile convulsions was 3.46 ± 0.7 year with insignificant p value in comparison to other groups. In agreement with our study **Rahman et al** [11] as they found the mean age for febrile convulsions 3 year .In contrary to our study **Hussain et al** [12] they found mean age of the sample was 1.8±1.04 years, In addition, **Potdar and Heydarian et al** [13,14] found the mean age for febrile convulsion was 2.8±1.5 year and 1.9±1.3 years respectively. This can be explained by genetic variation between the populations and geographical distribution among the countries.

In our study we found that there was no significant difference in sex between cases and control group. In agreement with our study **Hussain et al , Soheili et al , Potdar and Heydarian et al** [12,15,13,14] they found there was insignificant difference regarding sex between the groups.

In the present study, we found there was statistically significant difference in weight between febrile convulsions and other groups and significant decrease in HB,MCV and hematocrite. In contrary to our study **Vaswani et al and Heydarian et al** [16.14] they found there was insignificant difference in weight between febrile convulsions and febrile control group this may be due to difference in socioeconomic level between the countries and also the nutritional state.In addition most of our children with febrile convulsions have anemia may lead to retardation in weight gain.

In our study there was statistically significant increase in temperature in febrile convulsions with mean (39.59 ± 0.6) compared to control and idiopathic convulsions. In agreement to our result **Mohsenipour et al , Gontko-Romanowska et al and Ahmed et al** [17,18,19] they reported that there was significant increase in temperature in febrile convulsions than control group. In contrary to our result **Siroman et al** [20] they found that there was significant decrease in temperature in febrile convulsions than control group. This can explained by elevated brain temperature altering many neuronal functions also fever promotes pyrogen interleukin-1β (IL1β) synthesis, hyperthermia-induced hyperventilation and alkalosis that provokes neuronal excitability and seizure pathophysiology [4].

In the present study, we found that children with febrile convulsions had statistically significant lower in mean hemoglobin level (9.77 ± 1.4), MCV (72.41 ± 5.1) and hematocrit level (26.74 ± 4.1) than other studied groups. In agreement with our findings, **Sharif et al** [21] they found the presence of iron deficiency anemia was 45% in the convulsions group and 22% in the group with fever without convulsion. Children with febrile seizure had significantly lower hemoglobin and MCV. Moreover, **Kwak et al** [22] found children with febrile seizure had significantly lower hemoglobin and MCV. In contrary with our result **Derakhshanfar et al** [23] they showed that febrile seizure was less frequent in children with iron deficiency anemia comparing with other children, they noted that iron deficiency causes decrease in the level and activity of the exciting neurotransmitters including monoamine oxidase and aldehyde oxidase and leads to a reduction in excitation of the neurons and seizures.

Our result showed that children with febrile convulsions had statistically significant higher levels of platelet count (293.57 ± 36.6) in comparison with other groups. In agreement with our findings ,**Sharawat et al and Gontko–Romanowska et al** [24,18] they found children with febrile convulsions had statistically significantly higher levels of platelet count compared to control group. This can be explained by many studies have suggested that inflammation, which is intrinsic to the fever response, is involved in the generation of febrile convulsions, platelet indices have been shown to be an important component of the inflammatory response and the size and count of platelet is associated with the intensity of inflammation [25].

In our study there was significant higher level in TLC (7.75 ± 1.2) in febrile convulsions than fever without convulsions with no difference with idiopathic epilepsy. In line of our study **Biyani et al and Liu et al** [26,27] they found significant increase in leukocyte count level in febrile convulsions than control groups. In contrary to our result **Stöcklin et al and Hashim et al** [28,29] found that there was insignificant difference in TLC between febrile convulsions and control febrile group. our result can be explained by febrile convulsions associated with high fever which are characteristic for the high dynamic of infection development which associated with an increase in inflammatory factors such as CRP and leukocytosis [30].

inflammatory process was increasing slowly enough to get CRP at highest level**.** Our result can be explained by febrile convulsions associated with high fever which are characteristic for the high dynamic of infection development which associated with an increase in inflammatory factors such as CRP and leukocytosis [30]**.**

In our study we found no difference in serum lactate between febrile convulsions and other groups. In agreement of our study **Stöcklin et al** [28] they found no difference in serum lactate between the three groups.

In our study there was no difference in serum PH between the study groups. In agreement of our study **Kilicaslan et al** [32] compared children with febrile convulsions and children who presented with a febrile illness without convulsions and they found no significant difference in mean blood pH between febrile convulsions and control group.

In present study we found that there was significant decrease in HCO3 level in febrile convulsions compared with idiopathic epilepsy and significant increase in HCO3 level in idiopathic convulsions compared to fever control group. In agreement to our study **Stöcklin et al** [28] they found that significant high deficit in febrile convulsions compared to idiopathic epilepsy so serum HCO3

to small sample size of epileptic group 9

In our study we found CRP level (6.37 ± 0.9) was significantly higher in febrile convulsions than idiopathic epilepsy group with no difference with fever without convulsions. In agreement of our study **Abdullah et al** [31] found that there was significant high CRP level in febrile convulsions than epileptic seizure with no difference between febrile control group. In contrary to us **Liu et al** [27] reported that CRP was significantly lower in febrile convulsions than control group, this explained by them that children with febrile convulsions develop inflammatory process quickly enough that CRP level don´t reach to highest value while in children with fever without convulsions the

decrease in febrile convulsions compared to idiopathic epilepsy. This may be explained by respiratory alkalosis has been reported to be involved in hyperthermia-induced febrile convulsions in animal model [33] and was found to occur in children with febrile convulsions [34] so decrease the level HCO3 may considered as a compensatory mechanism to respiratory alkalosis.

In terms of the primary outcomes of the present study, we found that children with febrile convulsions had significantly higher levels of copeptin than idiopathic convulsions and fever without convulsions groups. At a cut-off value of 1.3, the copeptin yielded a sensitivity of 90% and specificity of 60% for the discrimination between febrile convulsions and fever without convulsions. Similarly, the copeptin yielded a sensitivity of 84% and specificity of 56% for the discrimination between febrile convulsions and idiopathic convulsions. In concordance with our findings, **Stöcklin et al** [28] they found circulating copeptin was significantly higher in children with febrile convulsions compared to febrile controls. Other study by **Abdel Salam et al** [35] found copeptin was significantly higher in febrile convulsions patients. In contrary **Stöcklin et al** [28] found that there was insignificant difference in copeptin level between febrile convulsions and idiopathic epilepsy this was may be due children in comparison to 83 child in febrile

convulsions ,in addition to difference in criteria of epileptic group in their study and between our study as in their study epileptic group include patient with secondary epilepsy due to structural defect (3 patient from 9) whose were excluded in our study. In our study we found there was no significant difference in copeptin level between the subtypes of febrile convulsions (simple, complex) with median (1.97, 1.51) respectively. In agreement to our study **Stöcklin et al** [(28)] they found that there was no difference in copeptin level between simple and complex febrile convulsions. In addition **Abdel Salam et al** [(35)] found decreased discriminative ability of copeptin between febrile convulsions subtypes.

CONCLUSION

Serum copeptin is a novel, promising, biomarker for febrile convulsions. The present study showed that serum copeptin was a significant discriminator of febrile convulsions from idiopathic epilepsy and fever without convulsions. The serum copeptin achieved fair diagnostic performance which highlights its future role in diagnostic algorithm for febrile convulsions.

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