Migration Letters

Volume: 19, No: S8 (2022), pp. 1372-1378

ISSN: 1741-8984 (Print) ISSN: 1741-8992 (Online)

www.migrationletters.com

Evaluation of the Diagnostic Utility of Serum Copeptin Level in Children with Febrile Seizures

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Abstract

Introduction: Between the ages of six months and five years, 2-5% of children experience febrile seizures, which are the most common type of convulsion in children. Pituitary hormone arginine-vasopressin (AVP) has been demonstrated to influence the thermoregulatory system in response to fever and convulsions. It has been determined that the C-terminal region of copeptin is a good indicator of the synthesis of AVP. Objective: The aim of the current study was to assess serum copeptin's diagnostic utility in febrile seizures. Patients and methods: A case-control study was conducted at Makkah hospital Emergency., Saudi Arabia A total of 46 patients were recruited and were divided into two groups; Febrile seizure group included 23 patients and febrile without seizures group included 23 patients. Results: There is significant higher copeptin value in febrile seizures group compared to febrile control without seizures group (P<0.05). Copeptin in diagnose seizure patients in febrile patients revealed a sensitivity of 82.6%, a specificity of 78.3% and 80.4% accuracy at a cutoff value >75 pg/ml. Conclusion: The distinction between a febrile seizure and one without a seizure can be made by serum copeptin. In patients with fever, serum copeptin with a cutoff value of >75 pg/ml was a useful diagnostic for seizure detection. As a diagnostic tool, serum copeptin functioned satisfactorily, suggesting a possible place for it in the febrile seizure diagnostic algorithm.

Keywords: *Serum Copeptin, Febrile Seizures, Children.*

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Introduction

Seizures that happen in children but are not brought on by an illness of the central nervous system are known as febrile seizures (FS). Between the ages of six months and five, 2-5% of children experience these convulsive episodes, which are the most prevalent in childhood. [1,2]. While the exact cause of febrile convulsions remains unclear, it is widely acknowledged that a complex interplay of inherited and environmental factors is likely to exist. Both the high temperature that accompanies febrile convulsions and the extracranial origin of fever are common physiological responses to illness. Among the possible causes of these convulsions are fever-induced cytokine release, which causes transiently abnormal brain electrical activity [3-5].

The pituitary hormone arginine-vasopressin (AVP) has been shown to play a role in the thermoregulatory response to seizures and fever. Although AVP is unstable in peripheral blood and hence unsuitable for diagnostic use, the C-terminal portion of copeptin has been discovered to be a robust indicator of AVP production [1]. Copeptin is a more persistent molecule in plasma and is largely eliminated by the kidneys, therefore it can be used as a stand-in for arginine vasopressin to signal an overactive system [6,7]. The aim of the current study was to assess serum copeptin's diagnostic utility in febrile seizures.

PATIENTS AND METHODS

A case-control study was conducted at Makkah hospital Emergency Room. A total of 46 patients were recruited and were divided into two groups: A) Febrile seizure group included 23 patients whoseparents/guardians or reported a convulsive episodeaccompanied by a high body temperature (>38°C), without prior afebrile seizure history. B) Febrile without seizures group included 23 patients who were age and Gender matched to case group, without a prior history offebrile or afebrile seizures.

Inclusion criteria: Age ranged from six months to six years. Both genders.

Exclusion criteria: Patients aged less than 6 months or more than 6 years. Children with infections of the central nervous system. Seizures associated with hypoxic ischemic encephalopathy. Disorders of the neurocutaneous system. Metabolic inborn error.

Every patient was subjected to comprehensive history taking and clinical examination. Neurological examination included pupil, level of consciousness, motor, sensory, cranial nerves, gait, as well as Glasgow coma scale (GCS), a measurement tool for assessing consciousness in critically unwell or traumatized patients.The subsequent ratings are added and categorized: Aminor brain injury is worth 13 to 15 points, a moderate brain injury is worth 9 to 12 points, and a severe brain injury is worth 3 to 8 points [7].

Laboratory investigations included:

CBC (complete blood count): CBC sample was drawn from venous blood that had been thoroughly mixed and anticoagulated with ethylene diamine tetraacetic acid (EDTA). The test was carried out within 6 hours ofreceiving the blood specimen. The experiment was carried out on an automated cell counter “Sysmex XN- 2000™ Hematology System” to calculate eosinophils, use (Japan's Sysmex Corporation) in conjunction involving the evaluation of peripheral blood smears stained with Leishman for a differential leucocytic count.

C-reactive protein (CRP): Quantitative determination performed by tarbidimetry on Cobas 6000 (c501). Autoanalyser (Roche Diagnostics, Germany) used detreated reagents supplied by manufacturer, according tomanufacturer recommendations.

Serum electrolytes included Na, K, and Ca, and were measured by indirect poteutrometry on Cobas 8000 (ISE unit) Autoanalyser (Roche Diagnostics, Germany) using dedicated reagents supplied by manufacturer, according to manufacturer’s recommendations.

Arterial blood gases were performed on Cobas 221 blood gas analyzer (Roche Diagnostics, Germany).

Test for serum copeptin: Concentrations of serum copeptin were assessed using an enzyme-linkedimmunosorbent test, and were quantified using ELISA technique and DL-CPP-Hu Company provided the kit. The foundation of the double antibody sandwich is a target assay that has more than two possible epitopes thatthe pre-coated capture antibody and the detection antibody can simultaneously recognize. This product uses Double Antibody Sandwich ELISA technique. The pre- coated antibody is an anti-Human copeptin monoclonal antibody, while the detection antibody is a biotinylated polyclonal antibody. The standard curve concentrations for the ELISAs were 1000 pg/mL, 500 pg/mL, 250

pg/mL, 125 pg/mL, 62.5 pg/mL, 31.2 pg/mL, and 15.6 pg/mL. In terms of sensitivity, the least detectable dose ofcopeptin is frequently lower than 5.3 pg/mL.

Standard venipuncture methods were used to collectthe blood and serum was extracted, as soon as possible derived from blood cells. Samples were centrifuged for 10minutes to remove the serum after being allowed to clot for an hour at room temperature. Samples were prepared to minimize bioactivity loss and contamination kept at - 20°C. Cycles of freeze-thaw were avoided. All of the chemicals, serum references, and controls were warmed to room temperature (20 to 27°C) before the test began.

Ethical Approval:

This study was ethically approved. Written informed consent was obtained from all participants. This study was executed according to thecode of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. 2015). Qualitative data were defined as numbers and percentages. Chi-Square testand Fisher's exact test were used for comparison betweencategorical variables as appropriate. Quantitative datawere tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t- test/ Mann-Whitney U test was used for comparison between groups. P value ≤ 0.05 was considered to bestatistically significant.

RESULTS

There was no statistically significant difference between febrile seizures group and febrile control group,regarding to sociodemographic studied ($P>0.05$), except body temperature was significantly higher in seizure febrile group (Table 1).

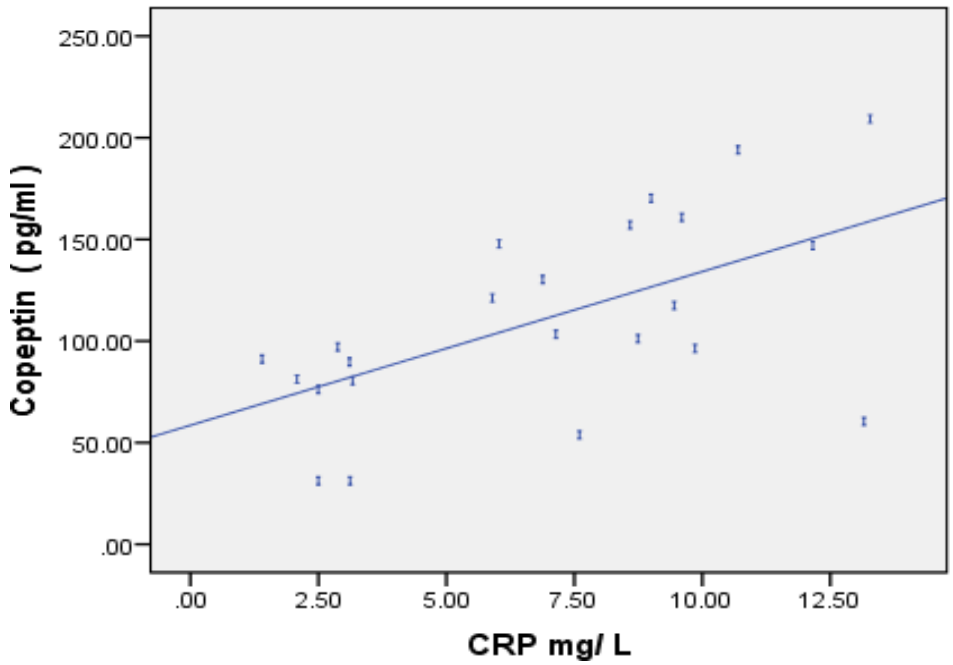
	Variable	Studied groups		Test ofSig.	P-value
		Febrile Seizures group (n. 23)	Febrile control without seizures group (n. 23)		
Age (year)	Mean ± SD	2 ± 1.4	2.5 ± 1.6	U	0.19
	Median (range)	1.6 (6 month-5 years)	2 (6 months-5 years)	1.3	
Sex	Females	11 (47.8%)	5 (21.7%)	χ 2	0.063
	Males	12 (52.2%)	18 (78.3%)	3.2	
Body weight(kg)	Mean ± SD	11.8 ± 3.2	13.5 ± 4.1	U	0.12
	Median (range)	11 (7-18)	13 (8-26)	1.6	

Body temperature(°C)	Mean ± SD Median (range)	39.2 ± 0.22 39 (38-39.7)	38.2 ± 0.16 38 (38-38.4)	U 17.1	0.0001*
Consanguinity	NegativePositive	21 (91.3%) 2 (8.7%)	18 (78.3%) 5 (21.7%)	χ 2	0.41
Duration of seizure (minute)	Mean ± SD Median (range)	3.7 ± 1.8 4 (1-10)	-----		

Table 2 showed that there was significant higher copeptin value in febrile seizures group compared to febrile control groupwithout seizures (P<0.05).

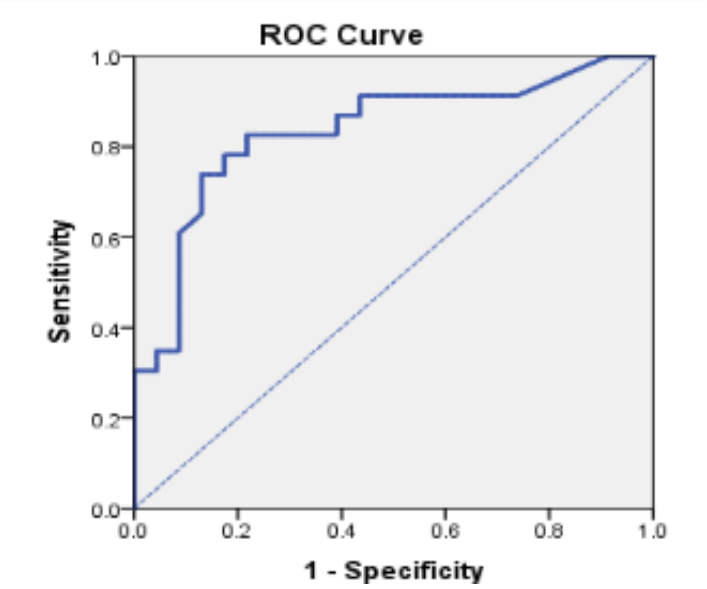
Variable	Studied groups		U	P-value
	Febrile seizuresgroup (n. 23)	Febrile control without seizures group (n. 23)		
Copeptin (pg/ml)Mean ±SD	110.8 ± 8.07	57.7 ± 3.02	3.9	0.0001*

In seizure febrile group there was significant direct relation between copeptin value and RDW,CRP ABG (P<0.05),otherwise there was no relation between other parameters



(Figure 1).

In febrile group: there was no relation between copeptin and age, weight, temperature, WBCs, Hb, MCV, MCH, RDW,PLT, CRP, Na, K, Ca, PH, in studied febrile group (Figure 2).



Copeptin in diagnose seizure patients in febrile patients revealed a sensitivity of 82.6%, a specificity of 78.3% and80.4% accuracy at a cutoff value of > 75 (pg/ml) Exploredthat copeptin at cut off value >75pg/ml good marker for detecting seizure in febrile patients (Table 3).

Cut off level (copeptin)	Sensitivity	Specificity	PPV	NPV	Accuracy
>75	82.6%	78.3%	79.2 %	81.8 %	80.4%

DISCUSSION

When examining the study groups' demographic information, it was found that there was no discernible difference in age or sex between the group having fever seizures and the febrile control group (without seizures) (P>0.05). Consistent with our research, Abd El-Moneim et al. (6) examined the potential of copeptin idiopathic convulsions as a biomarker for febrile convulsions in a case control study. Thirty-five children were involved in the study; thirty-five had idiopathic epilepsy, thirty-five had febrile convulsions, and thirty-five had fever without convulsions. The age or sex disparities between the studied groups were not determined to be statistically significant.

The study group's clinical data revealed a statistically significant difference between the group experiencing fever seizures and the febrile control group. On the other hand, there was no difference in weight or consanguinity between the group with febrile seizures and the group without them (P>0.05).

Additionally, Heydarian et al. (9) and Evers et al. (1) observed that there was no discernible weight difference between the febrile control group and the febrile group with convulsions, which is consistent with the current study.

Body temperature in the febrile seizures group compared to the febrile control group the febrile group without seizures (P<0.05). Mean duration of seizure per minute was 3.7 (SD 1.8) and range from one minute to 10minutes.

Regarding plasma level of copeptin in studied groups, it was revealed that a significantly

higher level ofcopeptin in febrile seizures group compared to febrile control group without seizures (P<0.05).

Abd El-Moneim et al. [6] showed that copeptin levels increased significantly when febrile convulsions and idiopathic epilepsy were compared with fever without convulsions. Furthermore, Abdullah et al. [10] discovered that copeptin and prolactin levels were statistically significantly higher in the febrile seizure and epileptic groups than in the fever without seizure and control groups.

Additionally, Stöcklin et al. [11] discovered that therewas no difference between febrile and epileptic seizures, and that circulating copeptin levels were significantlyhigher in children with febrile seizures (Median 18.9pmol/L [interquartile range 8.5-36.6]) compared to febrile controls (Median 5.6 pmol/L [interquartile range 4.1-9.4]). Moreover, in consistency with current study Salamet al. [12] showed that copeptin levels was significantly higher in febrile seizure (FS) patients than in febrileseizure control subjects without seizure patients.

Regarding the correlation between copeptin and age,weight, temperature seizure, duration, WBC, Hb, MCV, MCH, RDW, PLT, CRP, Na, K, Ca and PH, in studied febrile seizure group, it was revealed that there was significant direct relation between copeptin value and RDW, CRP and ABG. Otherwise, there is no relation between other parameters.

However, in febrile group, there was no relation between copeptin and age, weight, temperature, WBC, Hb, MCV, MCH, RDW, PLT, CRP, Na, K, Ca and PH.

In contrast to our findings, Abdullah et al. [10,13,14] found a significant correlation between the serumcopeptin level and the amount of time since the febrile seizure event.

To evaluate the serum's ability to serve as a diagnostic tool, ROC curve analysis was done copeptin todiscriminate febrile seizure, the current study showed thatat a cutoff value of copeptin >75 pg/ml revealed a sensitivity of 82.6%, a specificity of 78.3%% and 80.4% accuracy. The area under the curve (AUC) is 0.835 with (95%CI: 0.71-0.96), P<0.0001).

Consequently, the current study showed that copeptin at cut off value > 75pg/ml was a good marker for detecting seizure in febrile patients. In agreement with our study Abd El-Moneim et al. [6] showed that serum Copeptin produced results for differentiating between convulsive fever and non- convulsive fever with a sensitivity of 90% and a specificity of 60%. Additionally, Idiopathic epilepsy andfebrile convulsions showed a sensitivity of 86% and a specificity of 54% for serum copeptin. Also, Abdullah et al. [10] showed that 90% sensitivity and 60% specificity of serum prolactin at a cut-off point>20.8 ng/ml for the an episode of febrile seizuresis anticipated, while serum copeptin had 97% sensitivity and 70% specificity at a cut-off point>304 pg/ml. In contrast to prolactin, copeptin showed a greater overall ability to distinguish between children experiencing febrile seizures and controls (AUC 0.853, 97% vs. 0.757, 90%; p 0.001).

The current study was being a single center study, having a small sample size, and relatively short follow up period. Future studies may examine whether copeptin can differentiate between different whether the degree of the copeptin rise is related to clinical outcomes or epileptic syndromes, specifically the risk of developing epilepsy and the recurrence of febrile seizures. Further comparative it will take more extensive research to verify our findings and to identify risk factors of febrile seizure.

CONCLUSION

A novel and promising biomarker for febrile convulsions is serum copeptin. According to the current study, serum copeptin significantly distinguish between both febrile seizures and seizure-free febrile episodes. Serum copeptin had a passable diagnostic performance, underscoring its potential contribution to the diagnostic algorithm for febrile seizures.

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