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Review article

Role of copeptin in pediatric health and diseases

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Abstract

Copeptin, a precursor of vasopressin is released when the hypothalamic-pituitary-adrenal axis (HPA) is activated in response to stress. Copeptin secretion from the posterior pituitary gland is in equimolar amounts with arginine vasopressin, hence it reflects arginine vasopressin concentration and can be used as surrogate biomarker of arginine vasopressin secretion. Measurement of copeptin levels has been shown to be useful in a variety of clinical scenarios. Therefore it can be used as a novel diagnostic and prognostic biomarker in pediatric diseases. The purpose of the present article is to highlight the role of copeptin as a prognostic marker in different pediatric illnesses where it may help in early detection and diagnostic accuracy.

Keywords: Biomarker, copeptin, diagnostic, prognostic, pediatric diseases

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1. Introduction

Copeptin, a peptide of 39 amino acids, is a carboxy-terminal part of pre provasopressin. (AVP). It is a stable surrogate biomarker for AVP.[1]Copeptin is co-released from the hypothalamus in a 1:1 ratio with the hypothalamic stress hormone vasopressin, and hence secretion is activated not only by changes in plasma osmolality and circulating blood volume, but also by stress and inflammatory states. Thus it reflects the stress response during critical illness. Its plasma concentration has been associated with mortality in several acute disease states. Corticotropin-releasing hormone and AVP appear to have a synergistic effect in stress, resulting in adrenocorticotrophic hormone (ACTH) and cortisol release [2]. High cortisol levels reflect a higher degree of stress, but are dependent on the integrity of the HPA-axis. Copeptin appears to be superior to cortisol in determination of the stress level, as it is

challenging to measure free cortisol and it also has a strong circadian rhythm [3].In summary, together with adrenergic system and HPA axis, AVP system is also substantially implicated in the stress response against disrupted homeostatic balance and therefore copeptin has emerged as a promising biomarker of non-specific stress response. Thus, it can be used in the diagnosis, prognosis, risk stratification and therapeutic modalities of a variety of clinical conditions.

The purpose of this article is to summarize a handful of research done on copeptin and to discuss its role as a biological marker in the diagnosis and prognosis of various pediatric diseases which will help in early decision making in clinical practice.

Effects of copeptin and AVP in the circulation

When released into the circulation, AVP has three physiological functions. It mediates arteriolar vasoconstriction via the V1-receptor and exhibits an antidiuretic effect in the kidneys

via the V2-receptor [4]. A third AVP receptor, termed the V3 receptor is restricted to certain cells of the adenohypophysis and is involved in the secretion of ACTH [5]. Copeptin behaves in a similar manner to mature AVP in the circulation, with respect to osmotic stimuli and hypotension. In contrast to AVP, copeptin is very stable in the serum or plasma at room temperature and is easy and robust to measure [6,7].

Copeptin in pneumonia

In community acquired pneumonia copeptin predicts early deterioration and persistent clinical instability. Therefore, it can be used as a biomarker for early identification of high risk CAP patients who most likely benefit from early intensified management strategies.[8] It is a good predictor of short- and long-term mortality and superior to inflammatory markers.[9] In ventilator-associated pneumonia, copeptin is significantly elevated in non-survivors and moderately predicts survival [10].

Copeptin in sepsis

In patients with sepsis, copeptin concentration gradually increases with the severity of the disease. The level is higher in non-survivors as compared with survivors, suggesting copeptin can be used as a prognostic marker in sepsis [11]. In children with septic shock, vasopressin and copeptin levels may be good markers for severity of illness [12].

Copeptin in heart failure

The role of copeptin as a biomarker in patients with congestive heart failure has been described in several studies. Patients with chronic heart failure and high levels of copeptin had a significantly poorer long-term prognosis than patients who had low plasma copeptin concentrations. Its value is superior to that of BNP (B-natriuretic peptide) as a predictor of outcome in advanced heart failure patients [13,14].

Copeptin in febrile seizures

Circulating copeptin has high diagnostic accuracy in febrile seizures and may be a useful adjunct for accurately diagnosing postictal states when history and clinical presentation are equivocal [15].

Copeptin in nocturnal enuresis

Levels of copeptin are lower in children with nocturnal enuresis as compared with healthy patients while AVP levels were similar. This data may lead to development of a biomarker of NE that responds to pharmacologic treatment [16].

Copeptin in adolescents with primary hypertension

Higher serum copeptin levels, a surrogate for arginine vasopressin (AVP) release, is associated with elevated systolic and diastolic blood pressure and also with several components of metabolic syndrome including obesity, elevated concentration of triglycerides, albuminuria, and serum uric acid level. Role of serum copeptin as a novel marker of elevated blood pressure and predictor of metabolic syndrome needs more research [17].

Copeptin in hyponatremia and Diabetes Insipidus

Copeptin, has the potential to be used as a new marker in the differential diagnosis of hyponatremia. Plasma copeptin levels are significantly higher in patients with hypo- and hypervolemic hyponatremia compared with Syndrome of Inappropriate ADH ($P < 0.005$, respectively) and primary polydipsia ($P < 0.001$). The copeptin to urinary sodium ratio differentiates accurately between volume-depleted and normovolemic disorders. The combined information of plasma copeptin less than 3 pmol/liter and urine osmolality less than 200 mOsm/kg indicates primary polydipsia. Copeptin concentration < 2.6 pmol/L indicate central Diabetes Insipidus whereas concentrations > 20 pmol/L indicate nephrogenic DI [18].

Copeptin in neurological diseases

Copeptin, unlike the other brain biomarkers, is directly secreted into the systemic circulation. In conditions, like intracerebral haemorrhage, ischemic stroke, aneurysmal subarachnoid hemorrhage and head injury, copeptin concentration is elevated. In head injury, copeptin concentration elevated in peripheral blood is associated with mortality and poor neurologic outcome. Yu *et al.* reported that copeptin increases with severity of brain injury

and therefore, its measurements after brain injury provides an opportunity to distinguish patients with a one-year good or poor outcome. [19]Lin C et al studied the plasma copeptin concentrations of 126 healthy children and same number of children with acute severe TBI. Plasma copeptin level was identified as an independent predictor for 6-month mortality. The predictive value was similar to that of Glasgow Coma Scale (GCS) score for 6-month mortality and unfavorable outcome. Thus, plasma copeptin level represents a novel biomarker for predicting 6-month clinical outcome in children with TBI [20].

Limitations of copeptin

The overall mean serum copeptin level in children is (+SD) 14.6 ± 4.3 pmol/L. The mean copeptin level is significantly higher in boy (9.3 ± 5.9 pmol/L) as compared to girls (7.3 ± 4.8

should be taken into consideration while interpreting the result [21]. Given that the half-life of copeptin in the peripheral blood is approximately 45–60 min, [22] the time delay in blood sampling might affect the diagnostic accuracy. In response to respiratory alkalosis copeptin increases 5-fold, while exposure to hypoxemia, high PEEP, hemorrhage and psycho-emotional stress produces a more than 10-fold increase. Clinicians should be aware of factors influencing copeptin plasma concentrations [22].

Summary

Copeptin is a stable fragment of the AVP precursor. The measurement of copeptin appears to be a clinically relevant method for reliably assessing AVP plasma concentrations, which cannot be determined in routine practice. It appears to be superior to cortisol in determination of the stress level.

Table 1: Overview of studies investigating the role of copeptin in various diseases in children

Diseases	Author	Number of children	Outcome	References
Pneumonia	Fattah M A et al, 2013	81	Median copeptin levels were significantly higher in children who died as compared to survivors (89.5 vs. 28.1 pg/mL, $P=0.04$).	23
Community acquired Pneumonia	Wrotek A et al, 2014	311	Copeptin was significantly higher in patients with CAP (median 0.88 ng/mL) vs. healthy children (0.33 ng/mL; $p < 0.01$).	24
Febrile seizure	Stocklin B, et al, 2013	161	Copeptin was significantly higher in children with febrile seizures (median 18.9 pmol/L [8.5-36.6]) compared to febrile controls (5.6 pmol/L [4.1-9.4]; $p < 0.001$)	25
Nocturnal enuresis	Nalbantoglu B et al, 2013	88	Copeptin levels were significantly lower in patients (3.17 ± 1.15 pg/mL) who had bed-wetting 2 or more nights a week, than the control (4.95 ± 1.24 pg/mL)	26
Sepsis and septic shock	Lee JH et al, 2013	136	No difference in copeptin levels [1.2 (0.8, 1.8) vs. 1.5 (1.0, 2.2) vs. 0.9 (0.8, 1.2) ng/mL, $p = 0.14$] between control, sepsis and septic shock groups.	12
Primary hypertension	Edyta T B et al, 2010	84	Hypertensive patients had higher serum copeptin levels median, 267 (151.1–499.7 pg/ml)] than controls median, 107.3 (36.7–203.4 pg/ml)], ($p < 0.01$).	17
Tramatic brain injury	Lin C et al, 2013	126	Plasmacopeptin level was higher in patients than in healthy children (46.2 ± 20.8 pmol/L vs. 9.6 ± 3.0 pmol/L, $P < 0.001$).	20

pmol/L). Sexual disparity of copeptin level

- 1) Copeptin outperforms inflammatory markers like C- reactive protein and procalcitonin regarding their prognostic value in CAP. Thus, it improves the predictive properties of existing clinical scores and predicts early deterioration and persistent clinical instability in hospitalized CAP patients.
- 2) It is an independent predictor of mortality in VAP and helps to assess the disease severity to optimize clinical decision-making and therapy.
- 3) Unlike the AVP values which don't differ in patients with sepsis who survived and those who didn't survive, copeptin is higher in non-survivors compared to survivors. This suggests that copeptin could represent a prognostic biomarker in sepsis.
- 4) Copeptin and high-sensitivity cardiac troponin T levels, both single and combined, are powerful predictors of death and hospitalization in chronic heart failure.
- 5) Copeptin is increased in several acute neurological illnesses, such as acute ischemic stroke, spontaneous cerebral hemorrhage and brain trauma helps in neurologic prognostication. It may be a useful adjunct for accurately diagnosing febrile seizure in children.
- 6) Positive correlations between serum copeptin and body weight, body mass index, serum uric acid, triglycerides levels, TG/HDL ratio indicates that copeptin could be a new potential biomarker of insulin resistance and diabetes mellitus.

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