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Research Article

COPEPTIN (CT-proAVP): A PROMISING MARKER FOR EVALUATION OF EXACT TIME OF ONSET OF DIABETES INSIPIDUS

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A B S T R A C T

Copeptin (CT-proAVP), a stable surrogate of vasopressin precursor acts as a promising marker for evaluation of exact time of onset of diabetes insipidus associated with the surgery of craniopharyngioma, rathke's cleft cyst and suprasellar pituitary adenoma, and same time indirectly measures and predicts the severity of hypothalamic-pituitary neuronal system damage. Copeptin can prevent the significant clinical consequences resulting from misdiagnosis of serum sodium imbalances and fluid status in the subsequent post-operative period. Overall, copeptin helps in appropriate prescription for vasopressin analogue (e.g. desmopressin) in the post-operative period.

INTRODUCTION

In the field of neurosurgery (neurosurgically), resection of craniopharyngioma in the parasellar space involving the sellar, suprasellar and third ventricle;[1] rathke's cleft cyst[2] and pituitary adenoma surgery in the suprasellar area;[3,4] all these have the impulsive potential to develop vast group of salt and water disorders especially diabetes insipidus in both the short and long term process;[5–9] due to the manipulation of,[10,11] or damage to the hypothalamic-pituitary neuronal system (HPNS).[12] Injury or longer manipulation of the hypothalamic-pituitary neuronal system causes damage to the magnocellular arginine vasopressin (AVP) and oxytocin (OT) neurons.[13,14] Axonal injury of the hypothalamic pituitary neuronal system also leads to retrograde degeneration of the magnocellular neurons (MCNs)[12,14–17] which induces marked change in morphology and function of the neurohypophysis resulting in decreased levels of arginine vasopressin. Decreased levels of plasma AVP after axonal injury resulted from either inadequate synthesis by MCNs or failure of ectopic neural lobe formation; or loss of AVP storage and insufficient secretion by posterior pituitary.[18] Deficiency in AVP secretion from the posterior pituitary causes decrease ability of the kidney to concentrate urine, an abnormal renal response to AVP which finally culminates into a pathologic state referred as central diabetes insipidus (CDI).[19, 20] As AVP being the key hormone of water homeostasis and sodium being the main constituent of plasma osmolality, decreased levels of plasma AVP resulted in imbalances in water homeostasis and dysnatremic disorders.[21,22,23] Measurement of plasma AVP levels found to be helpful in differential diagnosis of dysnatremia and imbalances in water homeostasis as well as in diabetes insipidus (DI) but unfortunately, AVP measurement was cumbersome and not reliable.[24,25] Copeptin (CT-proAVP) which showed stoichiometric generation to AVP[25] was secreted in equimolar ratio to AVP[26] and copeptin levels mirror AVP levels.[27,28] Copeptin as proves to be a sensitive and stable surrogate of arginine vasopressin,[29] the measurement of CT-proAVP found to be useful in any diseases related to a disturbance of AVP release and/or electrolyte disturbances.[30–33] The major indications for CT-proAVP determination has been demonstrated in the diagnosis and differential diagnosis of DI,[34] and polyuria-polydipsia syndrome,[29,35] differential diagnosis of hyponatremia (such as syndrome of inappropriate ADH release [SIADH]).[30–32,36]

Moreover, copeptin as emerging biomarker proves to be a diagnostic and prognostic biomarker in various diseases state as well as proves to have optimal diagnostic accuracy in the diagnosis of diabetes insipidus of all types with a better sensitivity and specificity when compared to several other biochemical parameters. The measurement of plasma copeptin

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levels at the manipulation of hypothalamic pituitary neuronal system or during the resection of tumor from HPNS manipulation to complete tumor resection, can evaluate the exact time of onset of diabetes insipidus occurring in the intra-operative period or in the subsequent post-operative period. Same time, measurement of plasma copeptin levels help us to distinguish central diabetes insipidus totalis from central diabetes insipidus partialis which indirectly delineate the pituitary stalk injury from complete pituitary stalk section with partial pituitary stalk section. Finally, copeptin can prevent the significant clinical consequences resulting from misdiagnosis of serum sodium imbalances and fluid status in the subsequent post-operative period. Moreover, prescription for vasopressin analogue (e.g. desmopressin) is not essential in the impending postoperative period.

DISCUSSION

Copeptin (CT-proAVP), the carboxy terminal portion of arginine vasopressin (AVP), is a 39 amino acid-long glycosylated peptide with a leucine core segment that derives from the same precursor molecule as vasopressin.[37,38] CT-proAVP forms the C-terminal part of this precursor molecule, pre-provasopressin; and is produced in equimolar quantities with vasopressin itself through processing of the pre-provasopressin (Figure 1).[39,26] Copeptin along with AVP and neurophysin II are co-secreted at three sites: the posterior pituitary gland, the portal capillaries of the median eminence, and the cerebrospinal fluid of the third ventricle (Figure 2).[40] It is specific to the AVP-neurophysin II precursor but absent in the oxytocin-neurophysin I homolog. The function of copeptin is as yet imprecise i.e. physiological role of copeptin is still unknown. However, copeptin was recently suggested to serve as an important role in the correct structural formation of the vasopressin precursor, as a prerequisite which directs to efficient proteolytic maturation.[41] As copeptin (CT-proAVP) show stoichiometric generation,[25] it offers a simple and readily available method for AVP determination. Recent data show that copeptin levels mirror AVP levels.[28,27] In contrast to mature AVP which is rapidly degraded; 'e*x vivo'*, copeptin remains stable in serum or plasma at room temperature for at least 7 days and at 4^{o}C for at least 14 days, and can be quickly and easily measured.[25,26] Copeptin is not only easier to measure than mature AVP, but also remains undisturbed by therapeutically administered exogenous AVP and will certify that assessment of endogenous AVP production during AVP administration (similar to the detection of C-peptide in diabetes mellitus to measure endogenous insulin release under insulin therapy).[42] Copeptin can be detected from 50 µl of plasma or serum within 3hours; therefore results for the clinician are readily accessible.[27] Recently, a novel assay identified as sensitive sandwich immunoassay to measure copeptin in human serum or plasma and to quantify AVP secretion had been developed,[25,26] offering a potential alternative to available AVP assays. However, as of yet, the assay has mainly been used in the evaluation of copeptin as biomarker.[42] Copeptin results are available within an hour, which is crucial for any useful biomarker in the clinical settings. The measurements can be done on the "Kryptor"; a machine which is readily available in many Swiss hospitals.

In a study of 359 healthy individuals (153 men and 206 women), copeptin showed a relatively broad distribution with a median copeptin values of 4.2 pmol/L [range, 1.0 – 13.8pmol/L; 4.0 – 4.4 pmol/L at 95% confidence interval (CI)].[25] This distribution was similar to that reported by Robertson *et al* for AVP.[24] Stratification according to sex and age revealed lower values in females but comparable median values and distribution according to age for individuals 18–80 years of age.[25] Similarly, in another study of 20 healthy volunteers (8 men, 12 women) >18 years of age, documented a close correlation between plasma AVP and copeptin concentrations across a wide range of plasma osmolalities [Spearman's rank correlation coefficient (r_s) 0.49 for correlation between osmolality and AVP, and 0.77 between osmolality and copeptin, respectively].[43] Same study also documented that circulating copeptin levels reflect the activity of the thirst mechanism as well as the antidiuretic effect of vasopressin at the level of the target organ.[43] *In vivo*, copeptin values decrease rapidly after a water load, indicating similar kinetics as described for AVP in vivo.[44] Copeptin values increased distinctly after exercise, although the response varied among individuals. After a water load, the copeptin concentration decreased rapidly in a patient and returned to original values during the remainder of the day which demonstrated that copeptin shows identical changes during disordered water states as previously shown for AVP.[27] The main stimuli of copeptin in response to changes in osmolality and volume are identical to that of vasopressin.[27] Copeptin directly correlated with plasma vasopressin levels in healthy volunteers and critically ill patients.[45] Thus copeptin proved to be a sensitive and stable surrogate marker of AVP release.[29,42,46]

Emergent Role of Copeptin as Promising Marker

Different biomarkers were shown in clinical practice to improve the ability to diagnose, risk stratify and manage patients.[47] The emergent role of copeptin as prognostic and diagnostic biomarker in variety of diseases state has been mentioned.[46, 48] In a multicenter study, copeptin confirmed to be the strongest marker for mortality and morbidity in patients with heart failure after an acute MI.[49] In a study of 980 patients who had suffered an acute MI attack, the measured copeptin levels was highly elevated in patients who died or readmitted with heart failure, compared with survivors.[46] Copeptin attested to be significant independent predictors of death or heart failure. Highly elevated levels of circulating copeptin documented poor long-term prognosis in patients who suffered chronic heart failure.[50, 51] Recently, a prospective study documented that the combination of copeptin and high-sensitivity cardiac troponin T (hs-cTnT) levels ruled out acute MI with a sensitivity of 98.8% and a negative predictive value of 99.7%. Based on these studies, copepitn was recently listed amongst potential cardiac biomarkers by the National Academy of Clinical Biochemistry.[52]

As a *prognostic marker*, the role of copeptin was demonstrated in different clinical settings, such as in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), higher elevated copeptin levels was associated with prolonged hospital stay and long-term clinical failure independent of age, co-morbidity, hypoxemia and lung functional impairment in multivariate analysis.[53] In patients with lower respiratory tract infections (LRTI), the copeptin levels were significantly higher as compared with healthy controls, with highest levels in patients with community-acquired pneumonia (CAP).[54] Copeptin levels increased with increasing severity of LRTI, as classified by the Pneumonia Severity Index. In patient who died, copeptin levels on

admission were significantly higher compared to levels in survivors.[55] As a prognostic marker in medical intensive care unit (ICU), copeptin levels were independent predictors of survival in critically ill patients suffering from hemorrhagic and septic shock.[56] Copeptin levels increased with disease severity from systemic inflammatory response syndrome (SIRS) to sepsis and severe sepsis to septic shock. In the setting of ICU patients with SIRS to septic shock, the APACHE II score i.e. the standard clinical score in critically ill patients, gave similar values compared to copeptin.[48] In pediatrics infants with early-onset sepsis, chorioamnionitis and perinatal asphyxia, copeptin concentrations in cord blood were strongly related to factors associated with perinatal stress such as birth acidosis, perinatal asphyxia and vaginal delivery. Copeptin strongly correlated to perinatal stress with highest values found in neonates with perinatal asphyxia.[57]

Copeptin levels also have prognostic implication in diseases other than infections. Copeptin as an independent novel prognostic marker used for risk stratification of stroke patients,[58] cerebrovascular re-event after transient ischemic attack within 90 days.[59] Copeptin was associated with severity of stroke and lesion size; and high copeptin levels were highly predictive for poor functional outcome and mortality. Copeptin levels strongly predicted long-term stroke prognosis at its onset.[60] Copeptin provided identification of these high-risk stroke patients for whom secondary prevention and intensive rehabilitation can be directed to improve their outcome. Copeptin also predicted 30-day mortality comparable with that of Glasgow Coma Scale (GCS) and 90-day functional outcome after acute spontaneous intracerebral hemorrhage (ICH).[61] Increased plasma copeptin levels were associated with hematoma volume and an independent prognostic marker of mortality after ICH.[62] Copeptin used as complementary tool in prediction of disease outcome and cerebrovasospasm in patients with aneurysm subarachnoid hemorrhage.[63] Similarly, increased plasma copeptin levels were associated with mortality after traumatic brain injury (TBI).[63] Copeptin levels increased with increasing severity of brain injury.[64]

Moreover, copeptin served as a non-specific marker for disease severity in older patients presenting to the emergency department with non-specific complaints, irrespective of the final diagnosis.[65] Copeptin also provided independent and supplementary information to clinical risk scores, such as the Katz Index of Independence in Activities of Daily Living and the Charlson Comorbidity Index. In the emergency department, besides the established cardiac biomarkers such as BNP, NT-proBNP, derivates of atrial natriuretic peptide,[66] other peptides (for example mid-region pro-adrenomedullin,[67] ST2[68] and growth-differentiation factor-15);[69] copeptin is in competition with these novel markers to be used into clinical routine as potential prognosticators.[46]

As a *diagnostic marker*: Copeptin proved to be a promising new tool in the complex diagnosis of polyuria-polydipsia syndrome[34,29] with perfect differentiation of nephrogenic DI from all other etiologies of DI with a sensitivity and specificity of 100%, also in perfect differentiation of central DI patients from patients with primary polydipsia with a specificity of 95.8% and sensitivity of 94.1%, offering an alternative to the laborious and ambiguous water deprivation test. Similarly, copeptin proved to have diagnostic potential in the differential diagnosis of hyponatremia (e.g. Syndrome of inappropriate ADH secretion [SIADH]).[30–32,36] The measurement of copeptin has been useful in any diseases related to disturbance of AVP release and/or electrolyte imbalances.[30–33] In a clinical study of 38 patients, 33 patients after transsphenoidal surgery (20 with pituitary adenomas, four with craniopharyngiomas, five with rathke cleft cysts, three with other brain tumors, and one with hypophysitis) and 5 patients without transsphenoidal surgery (one with empty sella, one with hypoplasia of the pituitary, and three for other reasons) confirmed with diabetes insipidus, circulating copeptin levels reflected posterior pituitary integrity in these patient undergoing insulin-induced hypoglycemia for evaluation of anterior pituitary function.[35] Recently, the study of "copeptin after arginine infusion for the differential diagnosis of the polyuria-polydipsia syndrome "The CARGO-Study"-ClinicalTrials.gov identifier: NCT01879137" is under investigation.

As a whole, copeptin can be measured in the serum and plasma of healthy individuals and of patients presenting with different diseases state and beneficial to evaluate the clinical importance of copeptin as diagnostic and prognostic biomarker in variety of pathologies in which several other novel biomarkers and AVP secretion is alleged to be disturbed.

Copeptin better correlate to the diagnosis of DI than other biochemical parameters

The diagnosis of DI in the immediate postoperative period of neurosurgical patient was primarily based on both clinical and biochemical parameters. *Clinically*, the patient complained of an abrupt onset of polyuria and polydipsia, especially a craving for ice-cold water usually in the first 24 to 48 hours following neurosurgery.[21] This abrupt onset revealed the fact that the patients had intact thirst center[70] and were able to maintain urinary concentration fairly well until the number of AVP-producing magnocellular neurons in the hypothalamus had not undergone degeneration to 10% to 15%, after which permanent diabetes insipidus ensued.[21] Most of the patients with DI generally had intact thirst mechanisms; therefore, as long as the patients were able to drink adequate amount of water, they usually did not present with the signs and symptoms of either hyperosmolality or hypernatremia. Clinically, it was often necessary to limit fluid intake until hyperosmolality or hypernatremia developed in order to confirm a diagnosis of DI.[21] Consequently, longstanding or untreated DI has lead to deleterious effect which ranged from dehydration to lethargy, irritability and in the case of severe hypernatremia seizures.[71] Untreated DI in young children typically caused severe dehydration, vomiting, constipation, fever, irritability, sleep disturbance, failure to thrive and growth retardation.[20]

Moreover, when clinical symptoms of polyuria was suspected in immediate postoperative period in neurosurgical patient, central importance focused on several others potential clinical scenarios that can cause DI, before a clinical diagnosis of DI was confirmed. *First*, patients who suffered neurosurgical resection in the suprasellar region mainly received stress doses of glucocorticoids to prevent secondary adrenal insufficiency. In cases where steroid-induced insulin resistance produced hyperglycemia, the resulted osmotic diuresis from glucosuria can be confused with DI.[21] Similarly, adreno-corticotropin deficiency masked the signs of partial central diabetes insipidus and polyuria became manifested after corticosteroid replacement therapy.[72] Therefore, urine and blood glucose levels should be measured and any elevated glucose levels

necessarily brought under control to eliminate an osmotic diuresis as a cause of the polyuria. *Second*, excess fluids were sometimes administered intravenously during the perioperative period, which were then excreted appropriately postoperatively. If this large postoperative diuresis was matched with continued intravenous fluid infusions, an incorrect diagnosis of DI was made based on the resulting hypotonic polyuria. Therefore, if the serum [Na+] was not elevated concomitantly with the polyuria, the rate of parenterally administered fluid made slow with careful monitoring of the serum [Na+] and urine output, until diagnosis of DI confirmed by continued hypotonic polyuria in the presence of hypernatremia or hyperosmolality.[21,73]

Biochemical parameters: usually aid in the confirmatory diagnosis of CDI based on the demonstration of plasma hyperosmolality (>300 mosm/l)[74] associated with urine hypoosmolality (<300 mosm/l or urine/plasma osmolality ratio <1),[75] urine specific gravity <1.005,[76] and serum sodium ≥145 mmol/L.[75–79] While high urine output was a hallmark of the diagnosis of DI, different studies that were conducted showed diverse urine output thresholds concluding >2 mL/kg/h,[75] >30 mL/kg/day,[76] 2.5–18 L/day,[71,77,78,80] >250–500 mL/h for 2–3 consecutive hours,[5,79,81] 2.5–3.0 mL/kg/h[21] and >300ml/h for two straight hours.[6] These established definition of hourly urine output threshold remains in antagonism. Because of these variability in biochemical parameters, a study conducted by Sigounas *et al*.,[82] showed that the patients serum sodium levels >145 mmol/L in the first 5 days following neurosurgery had a much more higher risk of permanent DI compared to patients with serum sodium levels below 145 mmol/L (23.3 vs. 0 %, respectively). Similarly, another study conducted by Schreckinger M *et al*. supported that serum sodium levels >145mmol/L were highly significant for DI and gave 98% specificity when compared to serum sodium levels of 139 mmol/L for patients who did not develop DI.[6] Value of 138 mmol/L gave a 96 % sensitivity and a 50 % specificity in prediction of DI. In addition, the same study demonstrated that the change in the serum sodium levels before and after surgery of 2.5 mmol/L gives a 50% sensitivity and 80% specificity.[6] Even though these biochemical parameters aid in the confirmatory diagnosis of DI, unfortunately they demonstrated less sensitivity and specificity on comparison with copeptin in the diagnosis and differential diagnosis of DI.

Copeptin, a promising marker with diagnostic parameter proved to elucidate higher sensitivity and specificity in the differential diagnosis of hyponatremia.[36] This study showed that the ratio of plasma copeptin to urine sodium used to differentiate between hyponatremia in the syndrome of inappropriate antidiuresis (ratio <30 pmol/mmol) and hyponatremia attributable to edema-forming states or extra renal sodium loss (ratio >30 pmol/mmol).[36] Similary, this study has the discriminatory capacity for identifying primary polydipsia to 100%. Moreover, a study on copeptin proved to achieve optimal diagnostic accuracy in differential diagnosis of polydipsia-polyuria syndrome, with significant improvement in diagnostic accuracy of the direct water deprivation test (WDT).[29] This study reflected that copeptin had a 95% sensitivity and a 100% specificity in diagnosing central diabetes insipidus totalis; while a 100% sensitivity and a 86% specificity in diagnosing central diabetes insipidus partialis. Same study demonstrated copeptin also had a 100% sensitivity and a 100% specificity in diagnosing nephrogenic diabetes insipidus as well as a 86% sensitivity and a 100% specificity in diagnosing primary polydipsia. Similarly, another study showed that basal and stimulated copeptin levels were significantly lower in patients with diabetes insipidus compared with patients with intact posterior pituitary function (P = 0.003 and <0.001, respectively), and concluded that a stimulated copeptin level 45 min after insulin injection less than 4.75 pM had a 100% sensitivity and 100% specificity to detect diabetes insipidus.[35]

Recently, a prospective multicenter study on copeptin in the diagnosis and differential diagnosis of diabetes insipidus elucidated a single baseline copeptin level of > 20pmol/l perfectly differentiated nephrogenic DI from all other etiologies of DI with a sensitivity and specificity of 100%, rendering a water deprivation test unnecessary.[34] Additionally, a delta copeptin (difference between copeptin and copeptin upon osmotic stimulation, i.e. at a plasma sodium level >147 mmol/L) <2 pmol/L differentiated patients with central DI from patients with primary polydipsia with a specificity of 95.8%, a sensitivity of 94.1% and a positive likelihood ratio of 22.6.

Finally, in our review study plasma copeptin levels support to be one of the strongest contenders to evaluate the exact time of onset of diabetes insipidus in immediate neurosurgical operative period, and same time can measure and predicts the severity of hypothalamic-pituitary neuronal system.

Strong stimuli of Copeptin release perioperatively

A study showed that perioperative stress, pain and surgical trauma may cause an elevation of plasma AVP levels.[83] Below we discuss about the different stimuli occurring perioperatively in neurosurgical patient.

Preoperative stimuli: The main stimuli of copeptin in response to changes in osmolality and volume were identical to that of vasopressin.[27] Furthermore, a study investigated that the presence of preoperative anxiety and stress which were found higher among surgical patients referring as non-osmotic "stress" stimuli were major confounder of copeptin release.[84] A recent study supported that the measurement of plasma copeptin levels in patients with acute diseases appeared to add very little information to the work up of sodium imbalances and levels were similar in varying causes of mild sodium imbalances, this study also suggested that the non-osmotic "stress" stimulus in acute hospitalized patients was a major confounder of copeptin release and overruled the osmotic stimulus.[85] Moreover, another study documented that copeptin appeared to be superior to cortisol in determination of the stress level, as cortisol appeared to be further downstream in the stress response, had a strong circadian rhythm and was also challenging to measure as a free hormone.[48] This study also suggested that copeptin was one of the major hypothalamic stress hormones, which was stimulated by different stressors. Anything that throws the body out of homeostatic balance is primarily defined as stress.

Stimuli during ongoing surgery: Similarly, during the surgery, it had shown that pro-inflammatory cytokines, such as interleukin-1-β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), could activate the hypothalamic paraventricular cells to produce AVP which in turn lead to increased copeptin release.[86] Also during the surgery, despite the effective pain therapy and suppression of cortisol and

insulin response to surgical stimulus, the increase in AVP secretion is not affected by systemic or epidural morphine administration.[87]

Postoperative stimuli: The post-operative stress and pain contribute to increase levels of CT-proAVP release. Next the pro-inflammatory cytokines causes elevation of CT-proAVP release, such as elevation of circulating interleukin-6 after surgery.[88]

Evaluation of exact time of onset diabetes insipidus (DI)

A different perspective, revisited from copeptin in the diagnosis and differential diagnosis of diabetes insipidus,[29,34] patients with central diabetes insipidus readily distinguished from nephrogenic diabetes insipidus and primary-polydipsia with a single CT-proAVP measurement in the morning after minimum of 8 hours of water deprivation with direct or indirect measurement. Typically in neurosurgery, the patients undergoing neurosurgical procedure for craniopharyngioma, rathke's cleft cyst and suprasellar pituitary adenoma are nearly 8 hours of water deprivation preoperatively that causes the maximum stimulation of AVP and copeptin release. Additionally, the patient with craniopharyngioma, rathke's cleft cyst and suprasellar pituitary adenoma are under large neurosurgical interventions presenting with higher stress and anxiety levels and still remain under the main non-osmotic stimuli of copeptin release. Similarly, these patients are under continuous ongoing surgical trauma irrespective of any neurosurgical technique, causes higher level of copeptin release. Next with every neurosurgical procedure pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α remain to activate hypothalamic paraventricular cells to produce AVP and copeptin during and after surgery.

Ultimately, all these various factors such as water deprivation, stress, anxiety, pain, surgical trauma and pro-inflammatory cytokines support to be the major stimuli which lead to increase in copeptin (CT-proAVP) levels perioperatively, in these neurosurgical patients. Intraoperatively, this increased level of copeptin can be measured at the manipulation of hypothalamic-pituitary neuronal system and at various intervals during tumor resection as well as in immediate post-operative period. CT-proAVP levels measured at these intervals, if corresponds < 2.6 pmol/l[29] or a delta copeptin < 2 pmol/L[34] defines central diabetes insipidus totalis and conclusively discover the exact time of onset of central diabetes insipidus (Figure 3). This copeptin value of < 2.6 pmol/l or delta copeptin < 2 pmol/L indirectly delineate the complete pituitary stalk damage suggesting > 80% to 90% of magnocellular neurons (MCNs) undergone degeneration. And in the future this patient will suffer from persistent diabetes insipidus.

Whereas the CT-proAVP value between 4.0 - 4.4 pmol/l (at 95% CI)[25] which defines normal levels in healthy individuals exclude diabetes insipidus of HPNS origin and concludes that no pituitary stalk damage has occurred during the intraoperative period of tumor resection, this copeptin levels also signify that the patient is free from any other pre-morbid diseases condition that can cause higher stress level. If the CT-proAVP value is > 20pmol/l, it defines that patient already suffered from nephrogenic diabetes insipidus. Moreover, if the copeptin value ranges above the normal levels and below 20 pmol/l needs further investigation. Accordingly, in the subsequent post-operative period nearly at 16 hours (including a total of perioperative 16 hours), CT-proAVP-index i.e. Δ copeptin$_{[0800–1600\ h]}$ to S-Na$^+$ ratio (Δ copeptin is the change in copeptin between 0800 and 1600 h) of < 20 pmol/l/mmol/l defines central diabetes insipidus partialis whereas Δ copeptin to S-Na$^+$ ratio ≥ 20 pmol/l/mmol/l concludes primary polydipsia.[29,34] This distinguishing characteristic of copeptin from central diabetes insipidus totalis with central diabetes partialis can indirectly delineate complete pituitary stalk section with partial pituitary stalk section. Partial pituitary stalk section defines > 10% to 20% of magnocellular neurons are intact and the patients will only suffer from transient diabetes insipidus. Thus from the concept of Copeptin in the diagnosis and differential diagnosis of DI[34] and Polydipsia-Polyuria Syndrome,[29] the copeptin levels can evaluate the exact time of onset of diabetes insipidus associated with the surgery of craniopharyngioma, rathke's cleft cyst and suprasellar giant pituitary adenoma, and same time indirectly measures and predicts the severity of hypothalamic-pituitary neuronal system damage.

Perioperative factors influencing CT-proAVP levels

As the emergent role of copeptin as diagnostic and prognostic biomarker in variety of diseases state has been mentioned, following diseases such as SIRS, Sepsis, Severe Sepsis, Septic Shock; Cardiovascular diseases, i.e. Chronic Heart Failure and Myocardial Infarction (MI); Lower Respiratory Tract Infections, i.e. Community Acquired Pneumonia and COPD will have influences on the levels on CT-proAVP. Similarly, AVP Receptor Antagonist therapies and other diseases in which AVP has been shown to play an important pathophysiologic role will have an influence on CT-proAVP levels. *In vitro* study of "B.R.A.H.M.S CT-proAVP LIA", immunoluminometirc assay (ILMA) for the quantitative determination of C-terminal Pro-Arginine-Vasopressin (CT-proAVP, Copeptin) in human serum and plasma had found no influences of antimicrobial chemotherapeutics, vaso-active drugs, analgesics, anticoagulants and diuretics on the CT-proAVP measurement.[89] Additionally, non-interfering concentrations of hemoglobin, bilirubin, albumin and triglyceride were found with respect to CT-proAVP concentrations.[89] Similarly, another study suggested that during the surgery despite the effective pain therapy and suppression of cortisol and insulin response to surgical stimulus, the increase in AVP secretion is not affected by systemic or epidural morphine administration.[87]

Limitations of copeptin

As with most biomarkers there are certain confounding factors for the interpretation of copeptin levels. Significantly, the novel biomarker as copeptin levels must always be evaluated in the context of a careful clinical assessment. Furthermore, drugs may suppress the up-regulation of copeptin levels; for example, in a study in healthy individuals, copeptin levels was inhibited in a dose-dependent way upon prednisone treatment, suggested that corticosteroids influence copeptin levels.[90] Next, copeptin levels were found to be higher in the male individuals compared with female. Especially in men, there is a strong relationship between copeptin and decreased glomerular filtration rate, probably due to decreased renal copeptin clearance.[46] It has been reported that copeptin levels are higher in patients with renal insufficiency.[91] Secondly, the investigation of copeptin in all women should be carried out during the follicular phase of the menstrual cycle, when the

osmolal sensitivity is comparable between men and women.[92] Other false-positive and false-negative results may occur.[93] However, the utility of biomarkers is defined by the degree they improve clinical decision-making and add timely information beyond that of readily available information from clinical examination.[94]

CONCLUSION

Copeptin serves as a promising marker for the evaluation of exact time of onset of diabetes insipidus of HPNS origin. Copeptin has better sensitivity and specificity in diagnosis of diabetes insipidus of various etiologies when compared to several other biochemical parameters and clinical symptoms. Early diagnosis of diabetes insipidus in the immediate post-operative period can help surgeons and clinicians in the better management of patients and prevent significant clinical consequences resulting from misdiagnosis of serum sodium imbalances and fluid status. Copeptin also acts as a complementary tool to guide them which patients will suffer from transient diabetes insipidus and which will from permanent diabetes insipidus in early period after a neurosurgical procedure, and plan further management accordingly. Moreover, copeptin helps in the appropriate prescriptions of vasopressin analogue (e.g. desmopressin) in the subsequent post-operative period.

Conflict of Interest: None

Disclosure: None

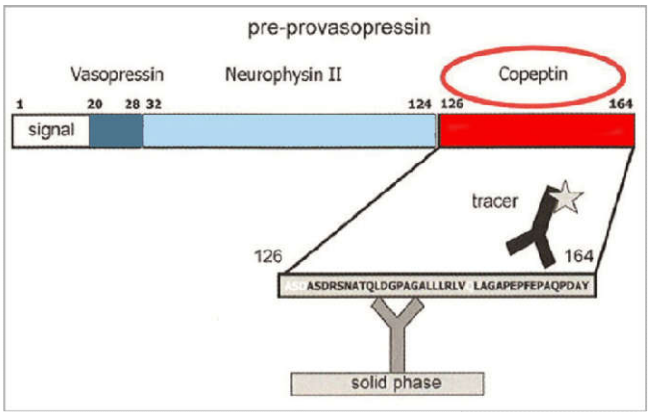

Figure 1 Copeptin (CT-pro AVP) protein.

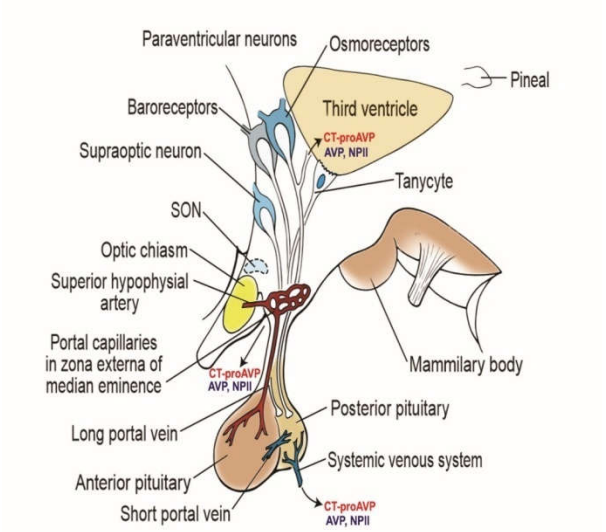

Figure 2 Synthesis of Copeptin and Vasopressor in the hypothalamic-pituitary neuronal system

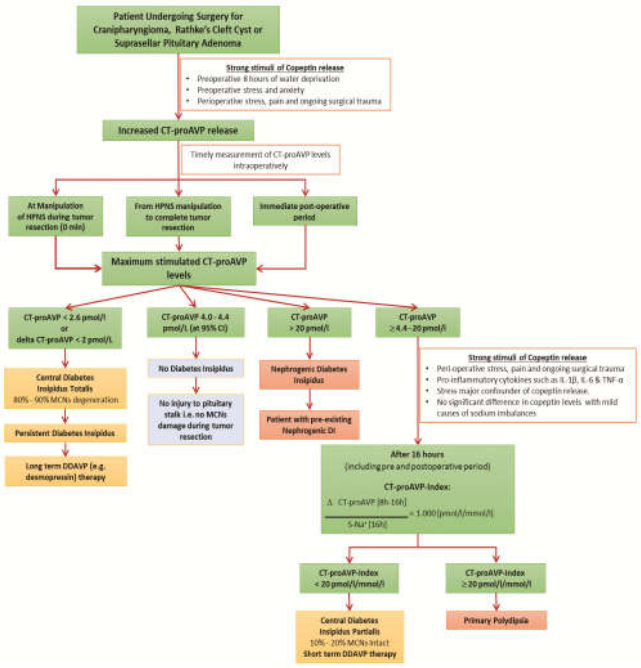

Figure 3 Prediction of exact time of onset of Diabetes Insipidus with Copeptin (CT-pro AVP)

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