Editorial Commentary

Changing the diagnostic approach to diabetes insipidus: role of copeptin

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Diabetes insipidus (DI) is characterized by polyuria and polydipsia. It can be caused either by deficit of vasopressin (central DI) or by renal resistance to its action (nephrogenic DI). The diagnosis of vasopressin deficiency can be confirmed by a serum osmolality >300 mOsm/kg and urine osmolality <300 mOsm/kg, while the differential diagnosis of different conditions presenting with polyuria and polydipsia with a serum osmolality <300 mOsm/kg requires a water deprivation test (1). Despite the fact that the water deprivation test represents the cornerstone for the diagnosis of DI (2), it is very distressing for patients and caregivers, exposes children to the risk of dehydration, it is time-consuming, its diagnostic accuracy is only 70%. Moreover, the following desmopressin test—used to evaluate the ability of the kidneys to concentrate urines in response to desmopressin—could be partially informative in patients with long-lasting polyuria and polydipsia.

In the past, Robertson *et al.* developed a radioimmunoassay for vasopressin in order to improve the sensitivity of water deprivation test but this assay was found to be difficult to manage in clinical practice for several reasons (3): over 90% of circulating arginine vasopressin (AVP) is bound to platelets and then its levels can be underestimated, and, on the other hand, if the platelets are not completely removed from the plasma samples or if the blood samples are processed after prolonged storage, the AVP levels can be found falsely elevated or variables. Moreover, after secretion, AVP presents a very short half-life (about 24 minutes). AVP is labile also if stored at low temperatures, and being of small size it cannot be measured by sandwich immunoassay but only by less competitive immunoassays.

The vasopressin derives from the cleavage of the pre-pro-vasopressin in vasopressin, neurophysin II and copeptin during its synthesis and axonal transport to posterior pituitary gland from the hypothalamus. Neurophysin II and copeptin are carriers of vasopressin and are stored in the neurohypophyseal vesicles until they are secreted (4). Differently from vasopressin, copeptin, the C-terminal segment of the AVP prohormone, has no known biological function but has several advantages compared to AVP making it a relatively stable surrogate marker of vasopressin secretion. While the assays measuring copeptin require very small amounts of serum or plasma (50 µL), the AVP assays needs 1 mL of plasma.

Other advantages of copeptin measurement assays are the lack of need of pre-analytical procedures, the possibility to obtain a result quickly (about 3 hours), and the low analytical detection limit (1.7 pmol/L). In addition, by these assays it is possible to detect serum or plasma copeptin in 97% of the healthy population and probably the most relevant advantage of copeptin, differently from AVP, is the stability in serum or plasma (at least 7 days at room

temperature) (4,5).

In recent years the knowledge and clinical use of copeptin has grown remarkably. In the 2015, a prospective study on different conditions associated with polyuria and polydipsia demonstrated that—without water deprivation test—a baseline level of copeptin >21.4 pmol/L allows to differentiate nephrogenic DI from other diagnoses with excellent sensitivity and specificity (100%) (6) suggesting that copeptin may replace water deprivation test accurately. This study, moreover, demonstrated that copeptin >4.9 pmol/L (at sodium levels >147 mmol/L) after water deprivation, allowed differentiation between primary polydipsia and partial central DI with a 94.0% specificity and a 94.4% sensitivity (6). Recently, a new multicenter prospective trial (7) showed that after stimulation with infusion of 3% saline (aiming at a sodium level >150 mmol/L), copeptin levels of >4.9 pmol/L had diagnostic accuracy of 96.5% (93.2% sensitivity and 100% specificity) in distinguishing between central DI and primary polydipsia, compared with only 76% for the classical water deprivation test. On the other hand, measuring copeptin during water deprivation test does not improve the diagnostic performance. Moreover, using a predefined ratio of Δ copeptin (8.00–16.00 h) to plasma sodium 16.00 h in distinguishing between primary polydipsia and central DI resulted in a lower overall diagnostic accuracy of the water deprivation test without copeptin, probably due to the lack of osmotic stimulation and therefore to the lack of a significant increase in the AVP or copeptin by thirsting alone (8). However, infusion of hypertonic saline requires serial controls to monitor on an appropriate increase in plasma sodium within the hyperosmotic range and despite the diagnostic advantages reported, it was associated with more adverse events than water deprivation alone; nausea was reported in over 70% of patients with thirst, vertigo, headache or malaise.

More recently, the same group proposed arginine-stimulated copeptin measurements as an alternative test in the differential diagnosis of DI in a large cohort of adult patients (9); arginine is already known as a stimulus for hormones released from the anterior pituitary gland (i.e., growth hormone and prolactin). The results of the study showed that arginine is a safe and a potent stimulator of copeptin secretion and the measurement of plasma copeptin levels after arginine stimulation is able to differentiate primary polydipsia from central DI with very good diagnostic accuracy. By pooling the data from the entire cohort an optimal accuracy of 93% was reached at a cutoff of 3.8 pmol/L copeptin at 60' (sensitivity 93%, specificity 92%). In addition, arginine infusion was well tolerated and safe. Even though very interesting and promising, this study has some limitations: the number of patients with partial DI (the most challenging diagnosis) was small, there were several outliers with very high levels of copeptin, the majority of affected patients were not naïve and were on treatment with desmopressin, suggesting that additional studies on larger newly diagnosed patients and a head-to-head comparison of hypertonic saline versus arginine cohorts are needed.

Are there data on children, and at what age from neonates to adolescent's hypertonic saline infusion or arginine tests can be performed? While the study by Winzeler *et al.* (9) includes 42 children with short stature and a mean age of 8.5 years (SD 2.9). As a control group, another study showed that children with pituitary dysfunction and DI have a lower basal copeptin (2.61±0.49 pmol/L) compared to those without DI (6.21±1.17 pmol/L) or to the control group (5.2±1.56 pmol/L) (10). In addition, obese children showed higher levels of copeptin compared to lean subjects and levels of 24-hour copeptin were related to urinary free cortisol in obese children (11). Furthermore, pubertal but not prepubertal boys showed higher levels of copeptin than girls, indicating that sex hormones could be involved in the regulation of levels of copeptin (11). Therefore, further studies on copeptin in large cohorts of children are needed. Moreover, preventing a significant extravasation of hypertonic fluid or arginine with the consequent potential localized focal necrosis, should not be underestimated.

Taken together, and waiting for copeptin to become universally commercialized, these data indicate that copeptin is a promising biomarker for the differential diagnosis of polyuria-polydipsia. Meanwhile, and until copeptin measurement will become available and refined, clinicians should be reassured that the differential diagnosis of polyuria and polydipsia remains possible without copeptin evaluation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Kliegman R, Stanton BMD, Geme J St., et al. Nelson textbook of pediatrics. 20th ed. Philadelphia: Elsevier Inc., 2016.
2. Di Iorgi N, Napoli F, Allegri AEM, et al. Diabetes Insipidus - Diagnosis and Management. Horm Res Paediatr 2012;77:69-84.
3. Robertson GL, Mahr EA, Athar S, et al. Development and Clinical Application of a New Method for the Radioimmunoassay of Arginine Vasopressin in Human Plasma. J Clin Invest 1973;52:2340-52.
4. Dobsa L, Edozien KC. Copeptin and its potential role in diagnosis and prognosis of various diseases. Biochem Med (Zagreb) 2013;23:172-90.
5. Christ-Crain M, Fenske W. Copeptin in the diagnosis of vasopressin-dependent disorders of fluid homeostasis. Nat Rev Endocrinol 2016;12:168-76.
6. Timper K, Fenske W, Kühn F, et al. Diagnostic Accuracy of Copeptin in the Differential Diagnosis of the Polyuria-polydipsia Syndrome: A Prospective Multicenter Study. J Clin Endocrinol Metab 2015;100:2268-74.
7. Fenske W, Refardt J, Chifu I, et al. A Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus. N Engl J Med 2018;379:428-39.
8. Christ-Crain M, Bichet DG, Fenske WK, et al. Diabetes insipidus. Nat Rev Dis Prim 2019;5:54.
9. Winzeler B, Cesana-Nigro N, Refardt J, et al. Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study. Lancet 2019;394:587-95.
10. Tuli G, Tessaris D, Einaudi S, et al. Copeptin role in polyuria-polydipsia syndrome differential diagnosis and reference range in paediatric age. Clin Endocrinol (Oxf) 2018;88:873-9.
11. Rothermel J, Kulle A, Holterhus PM, et al. Copeptin in obese children and adolescents: relationships to body mass index, cortisol and gender. Clin Endocrinol (Oxf) 2016;85:868-73.

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