Distribution of plasma copeptin levels and influence of obesity in children and adolescents

“DISTRIBUTION OF PLASMA COPEPTIN LEVELS AND THE INFLUENCE OF OBESITY IN THE PEDIATRIC AGE ”

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Abstract

In the last years, a more stable AVP surrogate, called copeptin, has been used as an adjuvant diagnostic tool in adults and seems to be promising also in the pediatric age. The aim of this study is to present plasma copeptin distribution in a large pediatric cohort and to observe the influence of fluid drinking and obesity on its measurement.

A cohort of 128 children and adolescents was split in two groups on the basis of nocturnal liquid thirsting (Group A) or free access of oral fluids in the 6-8 hours before the withdrawal (Group B).

At all the distribution percentiles copeptin levels were higher (***p<0.0001***) in Group A, as well as plasma sodium level and osmolality (***p=0.02*** and ***p=0.008,*** respectively). The influence of BMI on copeptin levels was investigated by dividing the cohort in non-obese (Group C) and obese children (Group D). Copeptin levels were higher in group D (***p=0.03***).

Conclusion**:** Copeptin measurement could be indeed an useful tool for the diagnostic pathway of dysnatremic conditions, but its interpretation should take into consideration the hydration status. Furthermore, it might be a promising marker also for obesity and metabolic syndrome, even if this hypothesis needs further studies to be confirmed.

Key words: copeptin, distribution, AVP related disorders, pediatric age, obesity

INTRODUCTION

Arginin-vasopressin (AVP) or anti-diuretic hormone (ADH) is the main hormone driving water and sodium homeostasis maintenance [1-10]. AVP-related disorders are represented by a heterogeneous group of conditions often characterized by severe neurological symptoms, mostly due to dehydration and dysnatremia, even life threatening if not promptly recognized and correctly treated.

An inappropriate AVP secretion associated with hyponatremia configures the syndrome of inappropriate antidiuretic hormone secretion (SIADH); its diagnosis is often challenging, as its laboratory features overlap with those of the cerebral/renal salt wasting syndrome (C/RSW), a rare and controversial but severe hyponatremic disorder mostly seen in patients with cerebral tumours [11-16].

Conversely, hypernatremia is the common finding of an insufficient AVP secretion, as observed in central diabetes insipidus (CDI), or insufficient AVP action, despite increased release, in case of AVP receptor resistance (nephrogenic diabetes insipidus, NDI) [17-20]. The biochemical features are not always helpful in distinguishing them from primary polydipsia (PP). AVP plasma concentration have been considered helpful in the diagnostic pathway of all these conditions, but the structural instability, its very short plasma half-life and, last but not least, the long lasting laboratory processing have limited its use in the clinical practice [29-32]. To differentiate them, a water deprivation test (WDT) is often required, even if the results interpretation can be cumbersome, especially in the presence of partial CDI [17-28].

Recent studies have regarded plasma copeptin investigation in the differential diagnosis pathway of either hyponatremic and hypernatremic AVP release disorders as it is a stable and fast-available measured surrogate of plasma AVP [33-35].

It has been shown that copeptin is very helpful in distinguishing between hypernatremic disorders (CDI, NDI and PP), but less helpful in hyponatremia (large overlap between SIAD/hyper - or hypovolemic hyponatremia). [36-48]. Similar data have been reported from our group in a small number of patients in pediatric age, even if these preliminary data need to be confirmed in larger cohorts [43].

Furthermore, some authors have reported the data about the use of copeptin measurement in hypertonic saline solution or arginine stimulation test with promising results in adults but to date there are no reported data about the use in pediatric age [49-50].

In pediatric age, copeptin plasma values have been considered as a prognostic factor in many conditions, such as septic shock, polmonitis, stroke, heart and kidney failure and brain traumatic injury [51-61]; higher copeptin levels have been described in insulin-resistant obese children [62].

However, few data exist to date about plasma copeptin distribution in the pediatric age, ranging between 2.4-8.6 pmol/L [8, 43]. Previous studies from our experience in 53 children not suffering from AVP-related disorders showed significant difference between the free access to fluids and the fluid thirsting for at least 6-8 hours population [43].

The aim of this study is to present plasma copeptin distribution in a larger pediatric cohort either by considering the fluid intake and the BMI.

MATERIAL AND METHODS

Study population

Plasma copeptin levels have been measured in 128 children and adolescents not suffering from any AVP related disease, referred to the Department of Pediatric Endocrinology of the Regina Margherita Children's Hospital of Turin in the period July 2016-May 2018.

The referral reason was suspected puberty or growth disorder which was not confirmed after hormonal basal and dynamic evaluation, all patients were free of other comorbidity, outpatient clinic and the access was planned after the first clinical evaluation by a pediatric endocrinologist.

Exclusion criteria were the presence of hypo or hypernatremia, abnormal urinary or plasma osmolarity, type I diabetes mellitus, hypo or hypercalcemia, hypokaliemia, hypo or hyperthyroidism, hypo or hypercorticism, kidney and heart diseases, recent episodes of nausea or vomiting, infectious diseases, brain traumatic injury, any treatment interfering with the AVP release system and nocturnal enuresis.

Plasma samples for copeptin investigation were collected early in the morning; the cohort was then split in two groups on the basis of nocturnal liquid thirsting at a home setting for at least 6-8 hours (Group A) or free access to liquids (limited to a maximum of 300 ml of water) in the 6-8 hours before the withdrawal (Group B).

The main anthropometric parameters height, weight and body mass index (BMI) have also 58 been considered in the studied papulation and allowed the distinction in non-obese (BMI <95° percentile, Group C) and obese children (BMI > 95° percentile, Group D [63], accordingly to BMI Cole percentiles.

Ethical approval from the Ethics Committee of the City of Health and Science University Hospital of Turin and written informed consent from the families were obtained before the study start.

Laboratory sample for plasma copeptin

Plasma samples for copeptin evaluation were collected into EDTA tubes. The peptide measurement was performed with an immunoluminometric assay (BRAHMS CT-proAVP LIA; B.R.A.H.M.S. GmbH, Hennigsdorf Germany) with lower detection limit 0.4 pmol/L and functional assay sensitivity less than 1 pmol/L. Intra and inter-assay have a CV% of <8% and <10% respectively.

Statistical analysis and graphs

Statistical analysis and graphs were performed by Graphpad 7 software (GraphPad Software, La Jolla, CA, USA) using T-Student for the means comparison.

RESULTS

Distribution of plasma copeptin levels in pediatric age

In the 128 children and adolescents (mean age 9.63 ± 3.36 years, 42 boys, 86 girls) with normal plasma sodium and osmolarity, mean plasma copeptin level was 6.76 ± 3.18 pmol/L (range 2-14.9 pmol/L).

The demographic and biochemical features of the studied population, divided in Group A (fluids thirsting for at least 6-8 hours) and Group B (free access to fluids) are represented in Table 1.

Plasma copeptin level in Group A was 10.26 ± 0.43 pmol/l whereas in Group B was 5.16 ± 0.18 pmol/L (***p<0.0001***) (Fig. 1).

Plasma sodium level was 141.3 ± 1.63 mmol/L in Group A, whereas 140.5 ± 1.81 mmol/L in Group B (***p=0.02***). Significant difference was observed between the 2 groups also for plasma osmolality (285.6 ± 5.89 mOsm/kg vs 283.5 ± 2.99 mOsm/kg respectively, ***p=0.008***).

Plasma copeptin distribution in percentiles for each group is represented in Table 2.

No difference was present between boys (n=42) and girls (n=86), for which mean copeptin 86 level was 6.96 ± 0.5 pmol/L vs 6.65 ± 0.34 pmol/L respectively (*p=0.61*).

Copeptin levels in obese children

The biochemical data relative to the non-obese (group C, 102 children, 28 boys and 74 girls, age 9.3 ± 3.32 years) and obese children (Group D, 26 children, 14 boys and 12 girls, age 10.94 ± 3.28 years) are represented in Table 3.

Plasma copeptin level was 6.4 ± 0.31 pmol/l in Group C, 7.931 ± 0.61 pmol/L in Group D (***p=0.03***, Fig. 2); no significant difference was observed for plasma sodium and osmolality between groups (Table 3).

DISCUSSION

AVP related disorders comprise different clinical conditions which may be life-threatening when hyponatremia or hypernatremia become severe. In case of hyponatremia, the differential diagnosis between the SIADH and C/RSW syndrome is challenging but fundamental, as their treatment is quite the opposite. Also, the distinction of partial diabetes insipidus and PP may be challenging and the management of the two conditions is quite different.

Thus, AVP plasma measurement may be useful in the diagnostic pathway of all these derangements, but its in vitro instability and its short half-life make the laboratory results almost useless. In the last years, the dosage of an AVP surrogate, called copeptin, has been used thanks to its higher stability and fewer required pre-analytical procedures [29-33].

Copeptin values in healthy adults range from 1 to 13 pmol/L and the serum levels are very sensitive to the osmotic and hemodynamic stimuli similarly to AVP. Copeptin levels significantly decrease even after little oral fluid intake as 200-300 mL or by hypotonic saline infusion whereas the water deprivation alone or followed by hypertonic saline infusion leads to copeptin levels increase [64, 65, 69]

Males show slightly higher values of copeptin with minimal difference in median values, whereas age or circadian rhythm do not interfere with its serum levels as well as food intake or menstrual cycle. In a previous paper, we showed the distribution of plasma copeptin levels in 53 children and adolescents without AVP-related diseases, indicating ranges between 2.4-8.6 pmol/L for the pediatric age [43].

In the current study we have enlarged our cohort of controls not suffering from any AVP-related diseases to

establish a more defined distribution in the evolutive age.

Plasma copeptin levels have been measured in a cohort of 128 children who were split in two groups on the basis of the orally ingested fluids; in the first group children who had been fluid thirsting for at least 6-8 hours were included, while free access to fluids was permitted in the other group. Copeptin, sodium and osmolality levels significantly differed in the two groups, even if sodium and osmolality were in the normal reference range in both groups. This strengthens the fact that even small fluctuations of sodium and osmolality within the normal reference range may lead to significant changes in the AVP release, which is really sensitive either to the hydration state [9,33-35]. Subjects with free access to fluids showed lower values all over the percentiles of the copeptin levels distribution than subjects with fluid deprivation, highlighting that oral intake, even of little fluid amounts, leads to significant copeptin values decrease and should be taken in consideration when interpreting its plasma levels.

Previous papers have reported similar mean copeptin levels, without showing a percentile distribution. In 2 studies on the use of copeptin as a marker for community acuired pneumonia and after brain traumatic injuries, fluid thirsting control cohorts displayed mean levels of 9.0 ± 2.7 and 9.6 ± 3 pmol/l respectively [51,55]. In 2 other papers analyzing copeptin as a marker for febrile seizures and in patients with type 1 diabetes mellitus, the control cohorts with fluid free access showed mean levels of 5.6 pmol/l and 5.56 ± 3.15, respectively [53, 59].

The relationship between copeptin levels and obesity [66-70], as well as its association to metabolic and cardiovascular risk factors, has been already explored in the adult age and in animal models. AVP normally acts through V1 receptor to maintain water and salt homeostasis, to control blood pressure variations and to promote the hepatic gluconeogenesis and glycogenolysis, whereas its action through the V3 receptor induces glucagon or insulin secretion. A positive correlation between plasma copeptin levels and the metabolic syndrome parameters was already decribed in the pediatric age [61] and higher copeptin levels have been described in obese children [62]. Our data, within a cohort of subjects with normal serum sodium and osmolality, indicate significantly higher copeptin levels in obese children than in the not obese counterpart. The significant differences 143 in the ages of the two groups might be explained by the fact that obesity onset mostly occurs in adolescence. Thus, plasma copeptin levels might be an important indicator of glucose metabolism dysfunction related to the BMI. However, further studies with larger cohorts and metabolic parameters analysis are needed to confirm this hypothesis.

Many Authors have investigated the copeptin levels in adults and their utility in the diagnostic pathways of AVP related diseases as well as their potential role as prognostic marker in various clinical conditions as acute miocardial injury, kidney and heart failure, stroke and sepsis [7,9,31-42,44-48]. While the direct measurement of copeptin can be helpful to promptly diagnose a nephrogenic diabetes insipidus (NDI), an osmotic stimulation by water deprivation test (WDT) or a hypertonic saline infusion are required to distinguish between primary polydipsia (PP) and central diabetes insipidus. Despite many authors have established its utility in the adult clinical practice, few 114 data on copeptin as a tool in AVP-related diseases

diagnosis have been produced so far and, overall, few data nowadays exist on plasma level distribution in developmental age [43, 51-62].

CONCLUSION

The present study further strengthens the fact that plasma copeptin level could be regarded as an useful indicator of AVP system function and water and sodium homeostasis; it should therefore be included in the diagnostic pathway of the pathological conditions involving the AVP release, especially when hypernatremia is present.

It has been demonstrated to be very sensible to plasma sodium and osmolality variations, as well as to orally or intravenous administered fluids.

In the present study we have presented plasma copeptin distribution in percentiles in a children population not suffering from any AVP release system disorders, in order to have normal copeptin values as references in the suspicion of AVP release disorders.

By considering the anthropometric variables in our control population, we can postulate that copeptin might be a promising marker also for other conditions such obesity and the metabolic syndrome in the pediatric age, even if this hypothesis needs further studies to be confirmed.

Authors contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by G.T. and E.M. The first draft of the manuscript was written by G.T. and all authors commented on previous versions of the manuscript. D.T. and S.E performed final statistical analysis. P.M and L.dS. performed the final revision of the manuscript. All authors read and approved the final manuscript.

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Abbreviations

ADH: anti-diuretic hormone

AVP: arginin-vasopressin

BMI: body mass index

CDI: central diabetes insipidus

C/RSW: cerebral renal salt wasting syndrome

NDI: nephrogenic diabetes insipidus

SIADH: syndrome of inappropriate anti-diuretic hormone secretion

WDT: water deprivation test

“What is Known”

- Copeptin use as a diagnostic tool in AVP-related disorders, such as diabetes insipidus or syndrome of inappropriate secretion of antidiuretic hormone, is well established in adults
- In pediatric age few studies are available but the preliminary data, including our previous study, seems to be promising.

“What is New”

- In this study we represent the distribution of copeptin levels in a pediatric cohort and show the significant influence of fluid ingestion on its plasma levels.
- Also BMI seems to be a significant variable on copeptin levels and may be used as an obesity marker in pediatric age