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To cite this version:

Laura Bonnet, Emeline Marquant, Julien Fromonot, Ilyes Hamouda, Julie Berbis, et al.. Copeptin assays in children for the differential diagnosis of polyuria-polydipsia syndrome and reference levels in hospitalized children. Clinical Endocrinology, 2022, 96 (1), pp.47-53. 10.1111/cen.14620 . hal-03660835

HAL Id: hal-03660835

https://amu.hal.science/hal-03660835

Submitted on 5 Apr 2023

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Copeptin assays in children for the differential diagnosis of polyuria-polydipsia syndrome and reference levels in hospitalized children

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Abstract

Objectives: Polyuria-polydipsia syndrome (PPS) is a common presentation in children but the differential diagnosis rests on burdensome water deprivation tests. The aims of this study were to determine a copeptin threshold to distinguish patients with central diabetes insipidus from those with primary polydipsia and to estimate the normal range of copeptin concentrations in children.

Design: Single-centre retrospective descriptive study.

Patients: Two hundred and seventy-eight children aged 2 months to 18 years who consulted for PPS ($N = 40$) or other reasons (control group, $N = 238$) at La Timone University Hospital in Marseille, France, between April 2015 and September 2019 and had a copeptin assay.

Measurements: Ultrasensitive copeptin assays on blood samples.

Results: Among the children with PPS, the mean copeptin concentrations were 1.72, 55.2 and 15.7 pmol/l in those with central diabetes insipidus ($N = 21$), nephrogenic diabetes insipidus ($N = 3$), and primary polydipsia ($N = 16$), respectively. Copeptin levels lower than 3.53 pmol/l were diagnostic of central diabetes insipidus with 100% sensitivity and 87.4% specificity ($p < .001$). The 5th–95th copeptin percentile range in the control group was 2.53–21.03 pmol/L. Copeptin levels were significantly higher in boys than in girls but there was no association with age, pubertal stage, body mass index, or the reason for consulting.

Conclusions: Our results indicate copeptin assays may be valuable in the differential diagnosis of PPS in children. Larger prospective studies are required to establish their accuracy in everyday clinical practice.

KEYWORDS
child, copeptin, diabetes insipidus, paediatric, polydipsia, polyuria, reference values

1 | INTRODUCTION

Polyuria-polydipsia syndrome (PPS) is a common reason for consultation in children. The most common diagnosis to exclude is diabetes mellitus (with a prevalence of 19.1 per 100,000 children in France).[1] A rigorous diagnostic procedure is then required to differentiate between the other principal causes (central diabetes insipidus, nephrogenic diabetes insipidus, and primary polydipsia) and adopt the most appropriate treatment strategy.

Arginine vasopressin (AVP) which is absent or deficient in central diabetes insipidus, cannot be used as a reliable biomarker because of its short in vivo half-life[2] and its instability in isolated plasma.[3] Moreover, the large volumes of plasma required for radioimmunoassay analysis and the complexity and length (>24 h) of the analyses[4] make AVP difficult to assess routinely paediatrics. Copeptin, a peptide hormone released with AVP in equimolar amounts,[5] is more stable, and concentration measurements are more reliable.[6] Chemiluminescence or immunofluorescence assays yield results in just a few hours on very small (50 μl) blood samples, with a detection threshold low enough to allow the analysis of diluted serum.[5,6]

Copeptin measurements have been used for several years for various indications, notably in adults as a predictive marker of morbidity in situations of physiological et psychological stress.[7–11] Copeptin levels also vary by sex,[6,12,13] renal function,[12,14] and body mass index (BMI),[15] with concentrations seeming to be elevated in children with obesity.[16,17] The normal range in adults was determined in 2006,[6,12] between 1 and 13 pmol/L. Copeptin has been used as a diagnostic tool for PPS since 2011, with a baseline level >20 pmol/l without prior water deprivation being diagnostic of nephrogenic diabetes insipidus.[18,19] However, baseline copeptin levels in patients with central diabetes insipidus and primary polydipsia largely overlap and cannot be used by themselves to differentiate the two diagnoses. Water deprivation or hypersaline infusion tests are still required, with copeptin levels below 4.9 pmol/l after either of the two supporting a diagnosis of central diabetes insipidus.[19]

In children, water deprivation tests are often poorly tolerated, with a risk of potentially severe dehydration and the need for intrahospital monitoring.[20] The use of copeptin in children has only been evaluated in a few small studies.[17,21–23] Normal copeptin levels, measured without water deprivation have been found to range from about 2.4 pmol/l to either 8.6 pmol/l[21] or 13.1 pmol/l.[17] Similar values have been reported in the control groups of several other paediatric studies evaluating copeptin in various pathologies.[22,23] These data were collected in children attending hospital for other medical conditions, which may modify copeptin values, even after exclusion of conditions known to significantly affect copeptin. Furthermore, the small number of patients considered means these thresholds are too uncertain to use in clinical practice.

The primary objective of this study was to determine a discriminating baseline copeptin level to differentiate between central diabetes insipidus and primary polydipsia in children with PPS. The secondary objective of the study was to measure copeptin levels in a control group of children without PPS.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a single-centre retrospective descriptive study of all patients aged 2 months to 18 years, who consulted in the multidisciplinary paediatrics department of La Timone University Hospital (Marseille, France) between April 2015 and September 2020 and whose copeptin levels were measured by ultrasensitive assay.

2.2 | Patients and data

Copeptin measurements were performed (i) in presentations of PPS or (ii) as part of routine care in the control group. The patients presenting with PPS were all inpatients sent to our department specifically for this reason. Their copeptin levels were measured in the morning before breakfast, without water deprivation, that is, with free access to water beforehand. The control group consisted of children seen as outpatients in the department during a planned hospital stay for additional tests as part of their treatment for chronic conditions other than PPS. These patients were advised to fast from midnight before their visit and blood samples were collected before breakfast. After informing the patients' families and provided the inclusion criteria were met, copeptin assays were performed along with standard laboratory tests, on the same heparin tube. All blood samples were immediately centrifuged and analysed in the hospital's biochemistry laboratory by automated immunofluorescence assay (B.R.A.H.M.S Copeptin proAVP KRYPTOR compact PLUS, Thermo Fischer Scientific) with a 0.69 pmol/L lower detection limit and <17% intra- and inter-assay variation. The same assay was used throughout the study.

The patients who consulted in the same period and for whom copeptin measure was not realized were not included. Samples taken during water deprivation tests were excluded, as were those taken in patients with confounding conditions (diabetes mellitus, untreated or poorly treated dysthyroidism, uropathy, renal failure with a GFR < 60 ml/min/1.73 m^2, electrolyte imbalance (Na < 135 mmol/l or >145 mmol/l, K < 3 mmol/l or > 5 mmol/l, corrected Ca < 2.2 mmol/l or >2.6 mmol/l), inflammation with CRP > 5 mg/l, and liver failure).

The following information was collected from the patients' medical records, in accordance with data protection regulations: age at the time of the test, sex, Tanner stage, age-adjusted BMI percentile, PPS status, presence of comorbidities, reason for hospitalization, urine and blood electrolyte levels and osmolarity.

Central diabetes insipidus was diagnosed by ongoing diuresis, impaired urinary concentrating ability (urinary osmolarity < 800 mOsm), increased serum sodium concentration and/or weight loss during a water deprivation test when it was clinically possible. If not, the diagnosis was made based on clinical and laboratory results (signs of dehydration, blood hyperosmolarity and low urine osmolarity) and/or imaging findings (pituitary anomaly) and a desmopressin test was directly performed in these cases. Primary polydipsia was diagnosed

if the water deprivation test showed normal urinary concentrating ability (urine osmolarity > 800 mOsm and absence of diuresis) without desmopressin stimulation.

2.3 | Statistical analysis

Continuous variables are presented as mean (standard deviation) and were compared between groups using *t* tests and Mann–Whitney tests. The *p* values reported are those of the *t* tests unless disagreement between the results of the two tests and a Shapiro–Wilk normality test both indicated that the data were not normally distributed. Categorical variables are presented as frequency (percentage) and were compared between groups using χ^2 tests. Statistical significance was defined as $p < .05$.

3 | RESULTS

A total of 459 copeptin assays were performed in 335 children during the study period and 278 satisfied the inclusion and exclusion criteria (Figure 1).

The study group consisted of 131 girls (49.4%) and 157 boys (50.6%), with an average age of 10 years and 6 months (±4.5). There were 238 patients in the control group and 40 patients in the PPS group.

Among the 40 children with PPS, 21 (53%) had central diabetes insipidus, 3 (8%) had nephrogenic diabetes insipidus, and 16 (40%) had primary polydipsia. The three children with nephrogenic diabetes insipidus, a 5-year-old girl and two boys, aged 6 months and 17 years, all had copeptin levels above 30 pmol/l (31.1, 100.8 and 33.7 pmol/l, respectively).

The median copeptin level in the 16 patients with primary polydipsia was 5.5 pmol/l [interquartile range (IQR): 2.7–10.2]. Among the 21 children with central diabetes insipidus, the median copeptin concentrations was 1.7 pmol/L (IQR: 1.0–2.0). Patients with primary polydipsia and central diabetes insipidus were comparable in all considered characteristics except age and sodium levels (Table 1). Primary polydipsia patients were significantly younger on average (3.1 vs. 9.6 years, $p < .001$) and had lower serum sodium levels (139.4 vs. 142.6 mmol/l, $p < .001$). Copeptin concentrations were significantly lower in the central diabetes insipidus subgroup (1.7 vs. 5.5 $p < .001$; Figure 2).

The characteristics of the control patients are presented in Table 2. The mean age in the control group was 10.3 years (±4.09), with a roughly equal number of girls (118) and boys (120). The median copeptin concentration was 7.6 pmol/l (IQR: 4.9–12.3); 5–95 percentile range, 2.53 to 21.3 pmol/l; Figure 2). Copeptin levels were significantly higher in boys than in girls (8.3 vs. 5.8 $p = .001$). Copeptin levels were not correlated with age, pubertal stage, or BMI. There were no significant differences in these variables between any of the subgroups defined by type of pathology (Figure 3): obesity (150/238 patients, 63%), endocrinopathy (28.6% of patients), neurological disease (3.4%) and gastrointestinal or liver disease (5%) (details in Supporting Information Appendix 1).

Copeptin concentrations below 3.53 pmol/l were diagnostic of central diabetes insipidus with a sensitivity of 100% and a specificity of 87.4% ($p < .001$). With an upper limit of 1.07 pmol/l on the other hand, the specificity was 100% and the sensitivity 28.6% (Supporting Information Appendix 3, Table 3).

Patients in the PPS and control groups were similar in terms of age, sex ratio and pubertal stage but differed significantly in terms of biomarkers and BMI (18 vs. 25, $p = .014$). Copeptin levels were significantly lower in the PPS group than in the control group

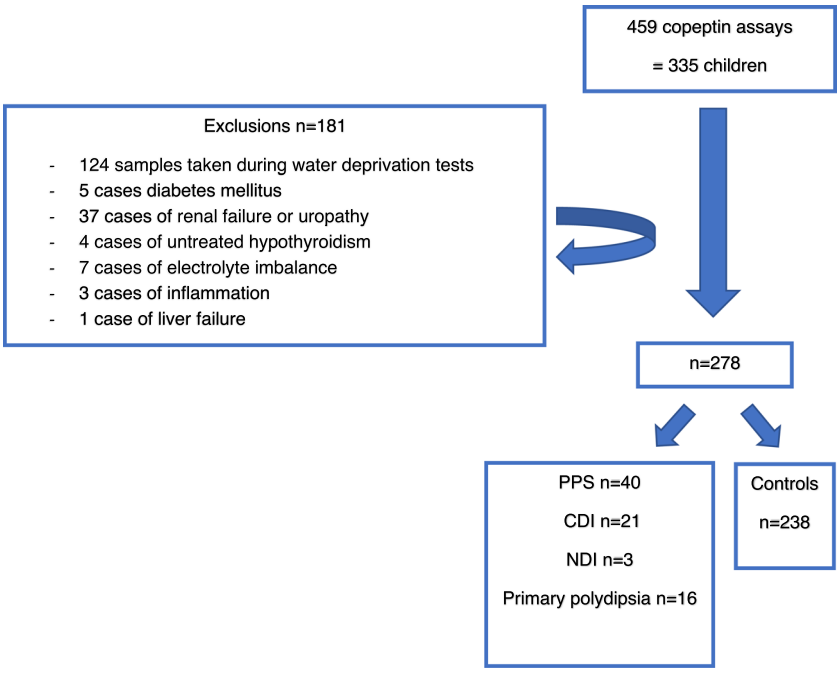

FIGURE 1 Study flow diagram. CDI, central diabetes insipidus; NDI, nephrogenic diabetes insipidus; PPS, polyuria-polydipsia syndrome

TABLE 1 Characteristics of patients with central diabetes insipidus and primary polydipsia (PP)

	Central diabetes insipidus (*N* = 21)	Primary polydipsia (*N* = 16)	*p*
Age (years)	9.6 (4.6)	3.1 (3.8)	<.001[a]
Male sex	12 (57%)	13 (81%)	.12[b]
BMI (kg/m^2)	19.6 (8.3)	16.0 (1.7)	.12[a]
BMI percentile	51.1 (38.4)	43.9 (36.2)	.59[a]
Na (mmol/l)	142.6 (2.6)	139.4 (1.9)	<.001[a]
Urinary osmolarity (mOsm)	347.9 (310.6)	361.9 (269.2)	.91[a]
Blood osmolarity (mOsm)	293.6 (10.2)	288.5 (4.9)	.08[a]
Blood proteins (g/l)	70.0 (7.1)	67.9 (7.2)	.42[a]
Copeptin (pmol/l)	1.7 (1.0–2.0)	5.6 (5.6–10.2)	<.001[c]

Note: Values are reported as mean (standard deviation), median (interquartile range) or number (percentage).

Abbreviation: BMI, body mass index.

[a]*t* test.

[b]χ^2 test.

[c]Mann–Whitney test.

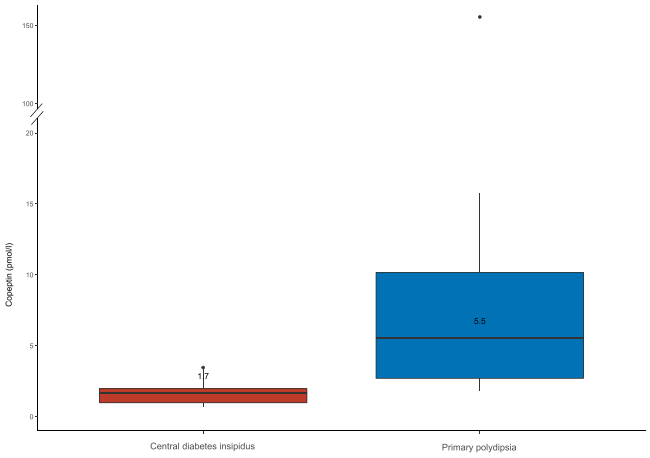

FIGURE 2 Box plot comparison of the distributions of copeptin concentrations in patients with central diabetes insipidus and primary polydipsia

(2.3 vs. 7.6 $p = .02$). Patients in the PPS group with primary polydipsia were similar to those in the control group in terms of copeptin levels (5.5 vs. 7.6 $p = .6$), despite non strictly similar sampling conditions in terms of access to water, but differed significantly in terms of BMI percentiles (44 vs. 79, $p = .002$; Table A1 in Supporting Information Appendix).

TABLE 2 Characteristics of control patients

	Control patients (*N* = 238[a])
Age (years)	10.3 (4.09)
Male sex	119 (50%)
Prepubertal	217 (91.2%)
BMI (kg/m^2)	24.8 (7.14)
BMI percentile	79.1 (33.44)
BMI > 97th percentile	140 (58.9%)
HOMA insulin resistance score > 2.4	90 (37.8%)
Na (mmol/l)	139.7 (9.5)
Blood osmolarity (mOsm)	283.8 (21)
Urine osmolarity (mOsm)	714.9 (288)
Blood proteins (g/l)	75 (5)
Reasons for consulting	
Obesity	150 (63.0%)
Endocrinopathy	68 (28.6%)
Neurological disorder	8 (3.4%)
Gastrointestinal disorder	12 (5%)

Note: Values are reported as mean (standard deviation) or number (percentage).

Abbreviations: BMI, body mass index; HOMA, homoeostatic model assessment.

[a]Details in Supporting Information Appendix.

4 | DISCUSSION

PPS is common in children but after excluding diabetes mellitus, the underlying cause can currently only be diagnosed by performing water deprivation tests, which are often poorly tolerated. Copeptin assays are part of standard clinical practice in adults, but rarely reported in children. The present study of 278 children is the largest reported to date. The objectives were to define copeptin thresholds for the differential diagnosis of PPS and to describe reference levels in control children.

The retrospective nature of the study meant that patients' access to water before copeptin measurements could not be standardized, which is a major limitation. Nevertheless, these data provide valuable information on copeptin levels in 'real-life' morning sampling conditions and may promote outpatient care for children with PPS in the future.

The level of the 5th copeptin percentile in the control group (2.5 pmol/l) is in agreement with the values reported by Tuli et al. (2.5–2.6 pmol/l) in studies of 40[21] and more recently 128 children.[17] However, the 95th copeptin percentile in our control group is much higher than reported previously for the upper limit of the normal range. This is because very high copeptin concentrations (>30 pmol/l) were measured in five patients in the control group with no identifiable underlying cause. While these five measurements are statistical outliers, there are no clinical grounds on which to exclude them. Among these five patients, one had Noonan syndrome with growth hormone deficiency, three had obesity (with a BMI above the age-adjusted International Obesity Task Force cut-off), and one had constitutional tall stature and was overweight. We found no common characteristic distinguishing these five patients from the rest of the control group as a possible explanation for their high copeptin levels. Indeed, one of the main limitations of the study is that patients were recruited in a paediatric hospital and therefore all had an underlying pathology.

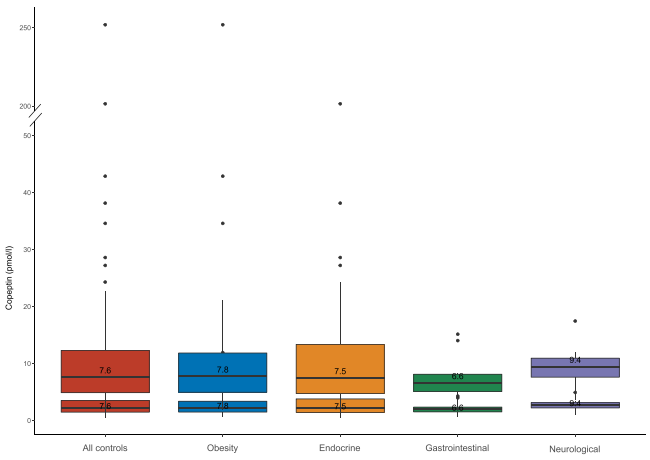

FIGURE 3 Box plot comparison of the distributions of copeptin concentrations in the different control subgroups

In keeping with results in the literature,[12] our study found that copeptin levels differed significantly between boys and girls. No significant variation with age was observed. This is consistent with the fact that copeptin levels do not seem to differ between adults and children. The three patients with nephrogenic diabetes insipidus had the highest copeptin levels, as described in the literature,[18,21,24] but the values measured here are even higher than those observed previously under similar measurement conditions. This may be due, at least in part, to differences in aetiology. Our three patients have complete hereditary nephrogenic diabetes insipidus, two due to AVP receptor 2 (AVPR2) mutations. Their baseline copeptin levels ranged from 31.1 to 101.8 pmol/l, which is similar to the value (106 pmol/l) measured by Tuli et al.[21] in their 10-year-old patient with familial diabetes insipidus. In contrast, the values reported for adults mostly correspond to patients with lithium-induced nephrogenic diabetes insipidus, whose baseline copeptin levels tend to be lower, ranging from 25.2 to 40.4 pmol/l[24] and 21.4 to 117 pmol/l.[18]

While other studies have found that copeptin levels were higher in patients with obesity,[16,17] there was no statistically significant correlation in this study between copeptin concentration and BMI. This may be because patients with obesity were overrepresented in the control group: more than half (59%) of these patients were obese, because our department is a specialist obesity unit, while the prevalence of overweight and obesity in France between the ages of 6 and 17 years are 17% and 4%, respectively.[25]

The fact that the department is referral centre for paediatric pituitary disorders also explains why the ratio of patients with central diabetes insipidus relative to those with primary polydipsia is so high.

In our study population, a copeptin threshold of 3.53 pmol/l in children consulting for PPS would have identified all cases of central diabetes insipidus without water deprivation tests, while a lower limit of 1.07 pmol/l would have excluded all cases of primary polydipsia. Between these two values, the imperfect sensitivity and specificity of copeptin concentrations means that a water deprivation test would nevertheless have been required for diagnosis, although potentially more accurate diagnostic methods could be considered. It may indeed be interesting to complement copeptin assays with measurements of other biomarkers, such as sodium, which was found here to

TABLE 3 Comparison of reported copeptin thresholds

	Tuli et al.[21]	Tuli et al.[21]	Present study
Control group	40	128	238
Normal copeptin range (pmol/l)	2.4–8.6	2.7–13.1	2.61–21
Children with PPS	15	–	40
Total number of subjects	55	128	278
Copeptin threshold to exclude CDI (pmol/l)	>3.5 (Se 75%, Sp 83.3%)	–	>3.53 (Se 100%, Sp 87.4%)

Abbreviations: CDI, central diabetes insipidus; PPS, polyuria-polydipsia syndrome; Se, sensitivity; Sp, specificity.

be significantly higher in patients with central diabetes insipidus than in those with primary polydipsia (correlation between the two variables is significant at the 5% level, plot in Supporting Information Appendix). A score based on a variety of laboratory results would strengthen the diagnosis or exclusion of central diabetes insipidus and would allow for shorter and safer water deprivation tests.

New techniques may also be able to complement copeptin assays to diagnose or exclude central diabetes insipidus without performing a water deprivation test. Winzeler et al. evaluated copeptin levels after arginine stimulation in a 5-year prospective diagnosis study of 92 adult patients with CDI or PP compared with 50 adults and 42 children healthy controls. A cutoff of 3.8 pmol/L copeptin at 60 min after arginine stimulation was 93% sensitive and 92% specific for CDI.[26] However digestive adverse events (nausea for 24%–58% of the patients, two patients excluded because of early vomiting) may limit the use of this test because of the risk of worsening dehydration and could stimulate AVP/copeptin release, leading to false negatives results in people with partial central diabetes insipidus.

5 | CONCLUSION

Copeptin, a readily quantifiable biomarker, seems to be a particularly valuable diagnostic tool in children with PPS. Based on our results, a morning fasting level greater than 3.5 pmol/l would exclude central diabetes insipidus without having to perform a water deprivation test. Similarly, a concentration below 1 pmol/l under the same conditions would be diagnostic of central diabetes insipidus. Larger prospective studies involving pathology-free children are needed to confirm these results and confirm the value of copeptin assays in everyday clinical practice.

ACKNOWLEDGEMENTS

Aderem to finance the translation work. This article was translated by Paul Guerry (Green Grow Scientific).

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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