RESEARCH

Copeptin is not useful as a marker of malignant disease in the syndrome of inappropriate antidiuresis

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Abstract

Objective: The syndrome of inappropriate antidiuresis (SIAD) is a common condition in hospitalized patients. It is crucial to establish the cause of SIAD, especially in order to exclude underlying malignancy. As malignant SIAD may be due to a paraneoplastic synthesis of arginine vasopressin, we hypothesized that its stable surrogate marker copeptin can be used as a diagnostic tool to differentiate between malignant and non-malignant SIAD.
Methods: Prospective observational study. We analyzed data from 146 SIAD patients of two different cohorts from Switzerland and Germany. Patients were included while presenting at the emergency department and underwent a standardized diagnostic assessment including the measurement of copeptin levels.
Results: Thirty-nine patients (median age: 63 years, 51% female) were diagnosed with cancer-related SIAD and 107 (median age: 73 years, 68% female) with non-malignant SIAD. Serum sodium levels were higher in cancer-related versus non-malignant SIAD: median (IQR) 124 mmol/l (120; 127) versus 120 mmol/l (117; 123) (*P*<0.001). Median (IQR) copeptin levels of patients with cancer-related SIAD were 11.1 pmol/l (5.2; 37.1) and 10.5 pmol/l (5.2; 25.2) with non-malignant SIAD (*P* = 0.38). Among different cancer entities, patients suffering from small-cell lung cancer showed the highest copeptin values, but overall no significant difference in copeptin levels between cancer types was observed (*P* = 0.46).
Conclusions: Copeptin levels are similar in cancer-related and non-malignant SIAD. Therefore, Copeptin does not seem to be suitable as a marker of malignant disease in SIAD.

Key Words

▶ hyponatremia
▶ paraneoplastic syndrome
▶ cancer
▶ lung cancer
▶ tumor

Introduction

Hyponatremia is the most common electrolyte disturbance in hospitalized patients (15–30%) (1) and is associated with increased morbidity and mortality (2, 3). One of its main causes is the syndrome of inappropriate antidiuresis (SIAD), characterized by water retention and secondary natriuresis (4, 5). SIAD can be caused by a variety of conditions (infections, CNS disorders, drugs, pain or stress (6)) and to large degree by cancers, whereby

it is postulated that arginine vasopressin (AVP) is produced paraneoplastically (6, 7, 8). Differentiation between these etiologies is important, especially in order to exclude or detect an underlying malignancy which is present in approximately one-third of patients with SIAD (9). So far, there are no evidence-based guidelines for differential diagnosis, and current diagnostic strategies are not well characterized. Therefore, a simple, reliable predictive marker would be of great interest.

Copeptin, the c-terminal part of the precursor peptide of AVP, is increasingly used as a reliable surrogate marker of the unstable AVP (10, 11). Copeptin has been postulated and evaluated as a diagnostic tool in hyponatremia but showed limited utility to differentiate between SIAD and other causes of hyponatremia, such as hypovolemic and hypervolemic hyponatremia (12, 13, 14). While in the latter two categories, copeptin levels are typically high; in SIAD (14) copeptin levels vary widely. In line with this, Zerbe *et al.* and later Fenske *et al.* described different SIAD subtypes according to different osmoregulatory defects (15, 16). The so-called subtype A, characterized by persistent high copeptin values (>38 pmol/l), was primarily observed in patients with lung cancer (16). These results point to the long-standing idea of malignant SIAD being caused by autonomous extra-hypothalamic production of AVP (e.g. in lung cancer tissue) (17, 18). Indeed, previous data indicated AVP mRNA and AVP peptide production in small-cell lung cancer cell lines (19) and in vivo studies showed significant elevations of AVP (20) and copeptin (21) in cancer patients.

Based on these findings, we hypothesized that copeptin levels are higher in cancer-related SIAD compared to non-malignant SIAD, and we aimed to explore whether copeptin may be used as a diagnostic marker for malignant disease in patients with SIAD.

Materials and methods

Study design

We analyzed data from 146 SIAD patients from two different prospective observational studies from Switzerland and Germany. Both studies evaluated the utility of copeptin in the differential diagnosis of hypoosmolar hyponatremia; the respective study designs have previously been described in detail (12, 14). All subjects gave informed consent to take part in the studies, and the study was approved by the Ethics Committee of Basel/Aarau and the Ethics Committee of the University of Würzburg.

Swiss cohort

From June 2011 to August 2013, 298 adult patients admitted to the medical emergency department of the University Hospital Basel and Kantonsspital Aarau with a serum sodium value of <125 mmol/l and serum osmolality of <280 mosmol/kg were recruited (NCT01456533) (14). Of those patients, 104 were diagnosed with SIAD and included in the present study.

German cohort

From March to November 2007, 106 adult patients admitted to the medical emergency department of the University Hospital of Würzburg with a serum sodium value of ≤130 mmol/l and serum osmolality of <280 mosmol/kg were recruited (NCT01341665) (12). Patients with impaired renal function (serum creatinine >3.0 mg/dl) and those whose previous pharmacotherapy could not be reliably specified were excluded. Of the remaining patients, 42 were categorized as SIAD and included in the present study.

Clinical and laboratory assessment

At admission, patient's medical history and symptoms, vital signs, body measures and fluid status were assessed and routine blood and urine samples were collected.

Additional blood samples for copeptin measurements were immediately drawn and stored at −70°C. All copeptin values were determined using a standard chemiluminescence sandwich immunoassay (B.R.A.H.M.S. Gmbh, Hennigsdorf/Berlin, Germany) (10). The lower detection limit of the assay was 0.4 pmol/l with a functional assay sensitivity (<20% interassay coefficient of variation) of 1 pmol/l.

Diagnostic criteria and classification of SIAD

The classification of SIAD was determined in a standardized way in both studies: an expert panel of at least two certified specialists was given access to all relevant clinical and laboratory patient information, covering the entire inpatient course. Importantly, new findings (e.g. new cancer diagnosis) arising during hospitalization and treatment response were included in the final classification.

Basic diagnostic criteria for SIAD included euvolemia, urine osmolality >200 mmol/l and normal adrenal and thyroid function. Further criteria were considered if available: urinary sodium >40 mmol/l, fractional excretion of urea (>35%) and uric acid (>12%).

Patients with SIAD were subclassified into cancer-related SIAD and non-malignant SIAD. In the non-malignant group, SIAD was further divided into the following categories: infectious SIAD, centrally induced SIAD, medication-induced SIAD and idiopathic SIAD.

For patients with cancer-related SIAD, the origin of the cancer and the disease stage (metastatic and non-metastatic disease) were assessed.

Study objectives

The primary objective of this study was to compare copeptin levels in patients with cancer-related SIAD to those with non-malignant SIAD. Further objectives included the comparison of copeptin levels between the different cancer types and SIAD categories.

Statistical analysis

Baseline characteristics are described using summary characteristics. The difference in the baseline values between the two cohorts was calculated by applying a *t*-test. To test for differences in copeptin levels between patients with cancer-related and non-malignant SIAD, a linear regression model was fitted indicating the presence of malignant disease as explanatory and log-transformed copeptin levels as dependent variable. Due to right-skewness of copeptin values, copeptin was log-transformed and normality was checked by inspecting QQ-plots. To further analyze whether copeptin levels are predicted by different cancer subtypes, a linear model was fitted with log-transformed copeptin values as dependent and cancer type as explanatory variable. Only patients with malignant disease were included in this analysis. A *P*-value of <0.05 was considered to be statistically significant. Analyses and graphics were performed using the statistical software package R (22) and GraphPad Prism7.

Results

Baseline characteristics

In Table 1, baseline characteristics of both cohorts are provided. Of the total of 146 patients, 92 (63%) were

Table 1 Descriptive table of the Swiss and German cohort.

	Total	Swiss cohort	German cohort
Characteristics			
Number of SIAD patients	146	104	42
Female, *n* (%)	92 (63%)	70 (67%)	22 (53%)
Median age (years)	69 (60–78)	71 (61–78)	67 (57–78)
Clinical parameters: median (IQR)			
BMI	23.4 (20.7–26.3)	23.5 (20.7–26.3)	22.9 (20.3–25.6)
Systolic BP, mmHg	136 (120–157)	143 (125–161)	116 (105–131.5)
Diastolic BP, mmHg	77 (67–84)	75 (66–84)	70 (65–79)
Heartbeats/minute	74 (65–84)	77 (67–86)	70 (60–80)
Laboratory parameters: median (IQR)			
Serum copeptin (pmol/l)	10.3 (5–26.6)	10.6 (5.4–27.2)	10 (4.4–20.3)
Serum sodium (mmol/l)	121 (117–124)	120 (116–122)	126 (122–128)
Serum osmolality (mosmol/l)	254 (247–262)	251 (242–258)	262 (257–266)
Urine osmolality (mosmol/l)	423 (327–546)	402 (326–496)	464 (343–594)
Categories of SIAD			
Cancer-related, *n* (%)	39 (27%)	19 (18%)	20 (48%)
Metastatic disease, *n* (%)	36 (92%)	19 (100%)	17 (85%)
Infections, *n* (%)	17 (12%)	9 (9%)	8 (19%)
Central, *n* (%)	23 (16%)	18 (17%)	5 (12%)
Medication, *n* (%)	45 (31%)	43 (41%)	2 (5%)
Others, *n* (%)	22 (15%)	15 (14%)	7 (17%)
Cancer types			
Lung (SCLC), *n* (%)	11 (28%)	8 (42%)	3 (15%)
Lung (others), *n* (%)	12 (31%)	6 (32%)	6 (30%)
Gastrointestinal, *n* (%)	7 (18%)	2 (11%)	5 (25%)
Hematological, *n* (%)	6 (15.3%)	1 (5%)	5 (25%)
Others, *n* (%)	3 (8%)	2 (11%)	1 (5%)

Data are presented as mean and interquartile range (IQR) or as percentage (%).
BMI: body mass index, BP: blood pressure, SCLC: small cell lung cancer, SIAD: syndrome of inappropriate antidiuresis.

Table 2 Descriptive table of patients with cancer-related and non-malignant SIAD.

	Cancer-related SIAD	Non-malignant SIAD	*P*-value
Characteristics			
Number of SIAD patients, *n* (%)	39 (26.7%)	107 (73.3%)	
Female, *n* (%)	20 (51%)	72 (68%)	0.09
Median age, years (IQR)	63 (59–69)	73 (60–80)	0.09
Clinical parameters: median (IQR)			
BMI	22.2 (20.4–24.8)	23.8 (21.1–26.3)	0.75
Systolic BP, mmHg	125 (116–142)	142 (122–160)	0.02
Diastolic BP, mmHg	72 (65–82)	77 (68–84)	0.24
Heart beats/minute	77 (64–83)	73 (65–84)	0.62
Laboratory parameters: median (IQR)			
Serum copeptin, pmol/l	11.1 (5.2–37.1)	10.5 (5.2–25.2)	0.38
Serum sodium, mmol/l	124 (120–127)	120 (117–123)	<0.001
Serum osmolality, mosmol/l	259 (250–266)	252 (243–258)	0.02
Urine osmolality, mosmol/l	499 (401–589)	393 (312–495)	0.01

Data are presented as mean and interquartile range (IQR) or percentage (%). *P* < 0.05 is considered to be significant.
BP: blood pressure, SIAD: syndrome of inappropriate antidiuresis.

female and the median age in the population was 69 years – without a statistically significant difference between the two cohorts.

Overall, the median serum sodium level was 121 mmol/l (IQR 117–124). According to the inclusion criteria, the median (IQR) serum sodium level was lower in the Swiss cohort, 120 mmol/l (116–122), compared to the German cohort, 126 mmol/l (122–128). German patients showed a higher median (IQR) urine osmolality compared to Swiss patients: 464 mosmol/l (343–594) versus 402 mosmol/l (326–496), respectively.

Overall, median (IQR) copeptin level was 10.3 pmol/l (5–26.6), with similar values in both data sets.

According to SIAD categories, 39 (27%) patients were found to have cancer-related SIAD with different proportions in the German (48%) and the Swiss cohort (18%). Similarly, frequencies of other SIAD categories also differed between the two cohorts, for example, medication induced SIADH was highly prevalent in the Swiss cohort (41%), but not in the German cohort (5%) (Table 1).

In the 39 patients with cancer-related SIAD, metastatic disease was present in 100% of the Swiss and in 85% of the German cohort. The remaining 15% of the German patients suffered from hematologic diseases whose progression is not defined by metastases.

Cancer-related versus non-malignant SIAD

Patients with cancer-related SIAD tended to be younger (median 63 years) and less often female (51%) compared to those with non-malignant SIAD (median 73 years, 68% female). Median (IQR) serum sodium levels were 124 mmol/l (120–127) in the cancer-related group

compared to 120 mmol/l (117–123) in the non-malignant group. Serum sodium and osmolality as well as urine osmolality were all significantly higher in patients with cancer-related SIAD than in patients with non-malignant SIAD (Table 2).

Median (IQR) copeptin levels were not higher in patients with cancer-related versus non-malignant SIAD: 11.1 pmol/l (5.2–37.1), with a range from 0.95 to 380 pmol/l versus 10.5 (5.2–25.2), with a range of 0.4 and 254.0 pmol/l, respectively (*P*=0.38, Fig. 1 and Table 2).

Copeptin values according to cancer types

When comparing copeptin levels between different cancer types (Fig. 2), overall no significant difference was observed (*P*=0.46). We found slightly higher values in patients with small-cell lung cancer compared to other cancer entities, but without statistical significance (*P*=0.43). The highest copeptin values were found in two patients with newly discovered, highly proliferative small-cell lung cancer (380 and 278.2 pmol/l).

Copeptin values in different SIAD categories

Within the different categories of non-malignant SIAD, there was a large overlap in copeptin levels, with high values up to >230 pmol/l in all categories (Fig. 3).

Discussion

The main finding of our study is that copeptin values vary widely in patients with cancer-related and non-malignant
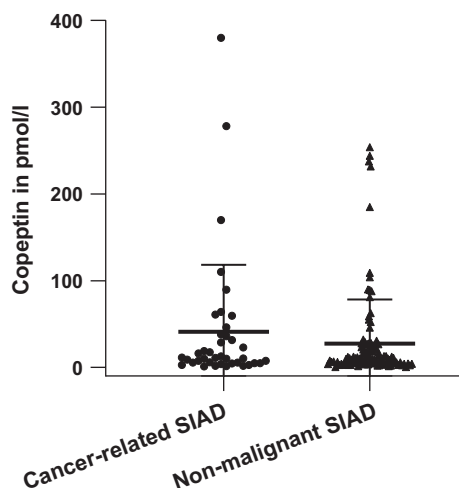
Figure 1
Copeptin values in patients with cancer-related and non-malignant SIAD. Boxplot: central line indicates the median; the upper and lower lines indicate the interquartile range.

SIAD and do not differ between the two groups. Similarly, we found no substantial difference of copeptin levels according to different cancer types or in the subcategories of SIAD.

The highest copeptin values (380 and 278 pmol/l) were observed in two patients with small-cell lung cancer. In fact, small-cell lung cancer is the best-characterized tumor entity of paraneoplastic AVP release by neuroendocrine tumor cells (19, 23, 24). The high copeptin values in these patients may therefore represent ectopic AVP production and correspond to the previously described
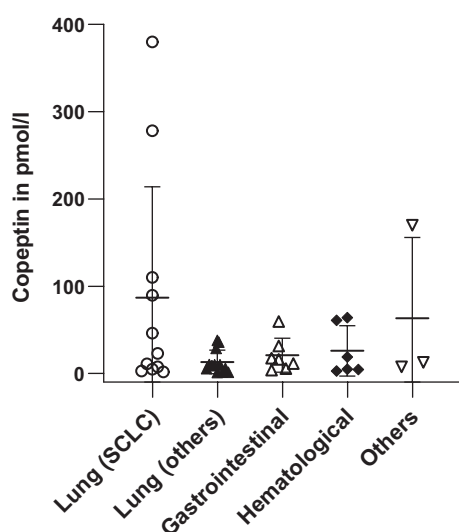

Figure 2
Copeptin values according to cancer types. Boxplot: central line indicates the median; the upper and lower lines indicate the interquartile range.
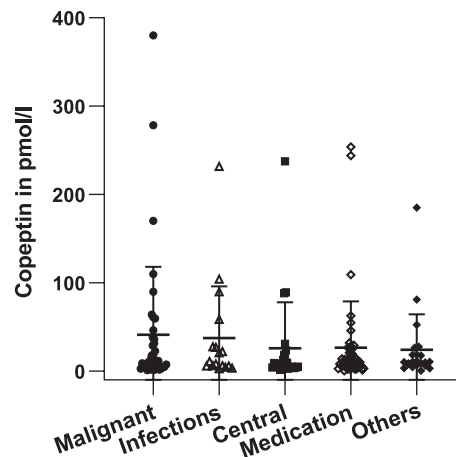

Figure 3
Copeptin values according to SIAD categories. Boxplot: central line indicates the median; the upper and lower lines indicate the interquartile range.

SIAD 'subtype A', characterized by erratic elevated AVP/copeptin levels (15, 16). Accordingly, in previously reported cases adjudicated to this subtype, copeptin levels were consistently above a cut-off of 38 pmol/l, and in four of five described cases even around 200–300 pmol/l (16). In contrast, in our small-cell lung cancer patients, the majority of patients had copeptin levels below 38 pmol/l. Thus, even in the subgroup of small-cell lung cancer, where all patients had active and mostly extended disease, copeptin levels were not throughout markedly elevated but varied widely. In the remaining cancer types, copeptin levels were in the IQR of 5.5–29 pmol/l.

There are several possible explanations for our findings. First, in the context of small-cell lung cancer and paraneoplastic phenomena hormones other than AVP (e.g. ANP) may play a role in hyponatremia (25, 26). Second, hyponatremia, and especially SIAD, is highly prevalent in patients with all types of cancer (5–30%) (8, 27, 28, 29). Besides ectopic hormone secretion, hyponatremia in cancer patients may be caused by the same conditions as in non-cancer patients: comorbidities, medication or symptoms such as vomiting, nausea, dehydration or stress. Of note, cancer patients are often polymedicated (e.g. chemotherapy such as vincristine and cisplatin, pain killers) or in an unstable condition and may, therefore, be particularly prone to hyponatremia (30). Third, irrespective of SIAD, copeptin is known to be elevated due to stress and acute conditions such as pneumonia, stroke or heart failure (31, 32, 33). All patients in our study were recruited in an acute setting when presenting at the emergency department. Thus, many of our patients might have had high copeptin values due to physical and

psychological stress. As previously shown by our group, the non-osmotic, stress-related copeptin stimulus in acute hospitalized hyponatremic patients may overrule the osmotic impulse (13, 14).

Of note, markedly elevated copeptin levels above 230 pmol/l were occasionally observed in all subcategories of non-malignant SIAD. These patients suffered from different health issues (i.e. acute exacerbation of COPD, nausea and vomiting, polymedication).

According to the Hyponatremia Registry, approximately one-third of euvolemic hyponatremia cases are cancer related with lung cancer as the most common cancer type (around 50%) (9). The high prevalence of cancer in SIAD is also demonstrated by our results with 27% cancer-related SIAD (of which 59% were due to lung cancer).

Interestingly, there were considerably more cases with cancer-related SIAD in the German compared to the Swiss cohort (48% vs 18%), and the cancer types varied between the cohorts. The main difference of our two cohorts was the severity of hyponatremia according to the inclusion criteria: serum sodium <135 mmol/l in the German and <125 mmol/l in the Swiss study. The high number of gastrointestinal and hematologic cancers in German patients with less pronounced hyponatremia corresponds to the findings of a Danish study observing that hematologic cancers are often associated with only mild hyponatremia (130–135 mmol/l), gastrointestinal cancer with moderate hyponatremia (125–129 mmol/l) and pulmonary as well as head and neck cancers with profound hyponatremia (<125 mmol/l) (28).

Indeed, the severity of hyponatremia may differ according to SIAD categories, as previously observed in our Swiss hyponatremia cohort: lower sodium values (<120 mmol/l) were more often associated with non-malignant hyponatremia categories (especially medication-induced SIAD) than higher levels (34). This observation, however, contradicts the finding of balanced hyponatremia severity in different SIAD categories as found in the international Hyponatremia Registry (9).

Otherwise, our results are mostly in concordance with the Hyponatremia Registry (9): patients with malignancy were generally younger, were more often male and had higher levels of urine osmolality than patients with non-malignant disease.

Some limitations have to be mentioned: the classification of hyponatremia and SIAD into different etiological categories remains a challenge as hyponatremia is often multifactorial and there is no reliable diagnostic standard. Therefore, even though adjudication was performed by experts and in a standardized manner,

patients may have been misclassified. Further, despite the large number of SIAD patients studied, only 39 (27%) had an active malignancy. Of those, cancer origin was very heterogeneous, leading to a very limited number in the various subcategories of cancer types.

A suitable diagnostic marker should be sensitive at an early stage of a cancer-related disease. Our patients with solid cancers were all in advanced stages, and we are therefore not able to draw conclusions about copeptin values as a diagnostic tool in an early phase of disease.

Finally, copeptin measurements were performed in an acute setting, where the stress-induced copeptin stimulus may overrule or confound the paraneoplastic or osmotic stimulus.

The strength of our study comprises the prospective data collection which allowed insights in the distribution of copeptin values in well-characterized SIAD patients with and without malignancy.

In summary, copeptin levels widely overlap in patients with cancer-related and non-malignant SIAD. This may be explained by the heterogeneity of SIAD and the multifarious factors leading to unspecific copeptin elevations in the acute setting. The use of copeptin as a marker to detect cancer-related disease in SIAD patients can therefore not be recommended.

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