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Lab bulletin

Copeptin

Polyuria-polydipsia syndrome: improved differential diagnosis
Pituitary surgery: easy monitoring for vasopressin deficiency
Traumatic brain injury: reliable follow-up for Hypopituitarism

The challenge in the diagnosis of the polyuria-polydipsia syndrome is differentiating between cases of primary polydipsia and diabetes insipidus. The diagnostic method of choice would be direct vasopressin determination, but the molecular characteristics of vasopressin make such measurement very complex and error-prone, hence unreliable. Consequently, „direct vasopressin testing" has not been established as a diagnostic routine. Now, a single Copeptin measurement can immediately distinguish central diabetes insipidus from nephrogenic diabetes insipidus (figure 2). Thus Copeptin measurement reduces the burden of the water deprivation test for the majority of patients and improves patient management within the clinic (2,10).

Copeptin is formed from the C-terminal portion of the vasopressin prohormone and is released in equimolar quantities with vasopressin itself through processing of the prohormone (Fig. 1).

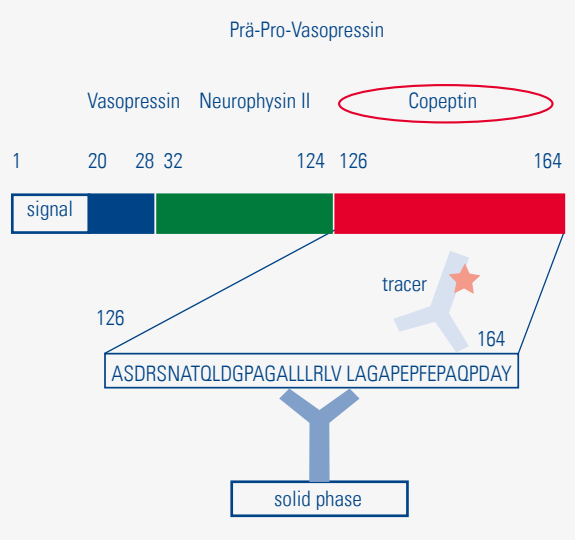


Fig. 1:
Schematic representation of the structure of pre-provasopressin
In addition to ADH, the preprohormone of ADH also contains two further peptides, neurophysin II und copeptin. Copeptin is located in the C terminal portion and can be measured reliably and simply by means of a sandwich immunoassay.

Vasopressin (ADH) and Copeptin show a significant correlation in several studies. The behaviour of Copeptin in response to changes in osmolality and volume, the main stimuli of vasopressin secretion, is identical to that of vasopressin (4,7). The physiological importance of Copeptin is still largely unknown.

Copeptin as a technically superior marker has replaced the determination of vasopressin (ADH) in the investigation of diabetes insipidus.

Reliable differentiation of central or nephrogenic diabetes insipidus from primary polydipsia is not possible without direct measurement of the Copeptin; direct measurement of the Copeptin during the water deprivation test is therefore recommended to facilitate differential diagnosis.

Copeptin offers the following advantages over the determination of vasopressin

- Vasopressin is 90 % bound to platelets. For this reason vasopressin concentrations are normally significantly lower than CT-pro AVP levels, due to the large quantity of platelet-bound vasopressin that is removed from the sample on centrifugation. The centrifugation mode influences the plasma platelet count and hence the vasopressin concentration in the sample.

  In the event of insufficient centrifugation, platelet-bound vasopressin remains in the sample and leads to falsely elevated vasopressin levels.

- Because of its small molecular size (9 amino-acids), vasopressin cannot be measured in a sandwich immunoassay, but only by means of a competitive immunoassay. This leads to poorer correlations in the lower concentration range, where vasopressin assays are no longer able to differentiate well.
  Copeptin can be determined in 97 % of healthy persons, whereas vasopressin is often not detectable in persons with low or medium serum osmolality.

Copeptin is stable in Serum or plasma at room temperature for at least 3 days while plasma ADH is unstable even frozen at -20°C.

The following diagnostic algorithm has been developed for the investigation of polyuria-polydipsia syndrome; in particular, it also covers the difficult differentiation of primary polydipsia from partial central diabetes insipidus (Fig. 2):

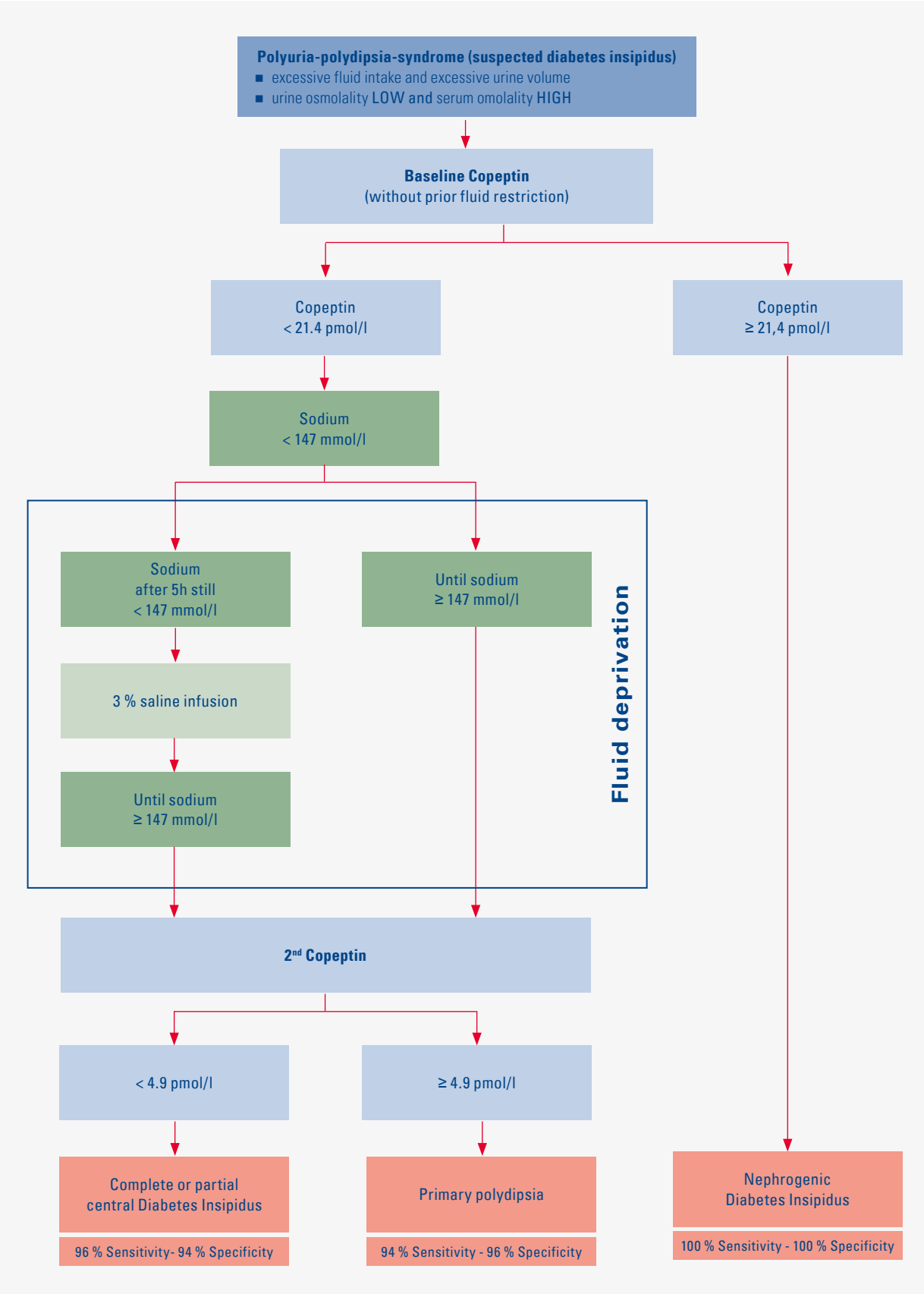


Fig. 2:
Algorithm for differential diagnosis of polyuria-polydipsia syndrome using Copeptin in patients with suspected diabetes insipidus [9]

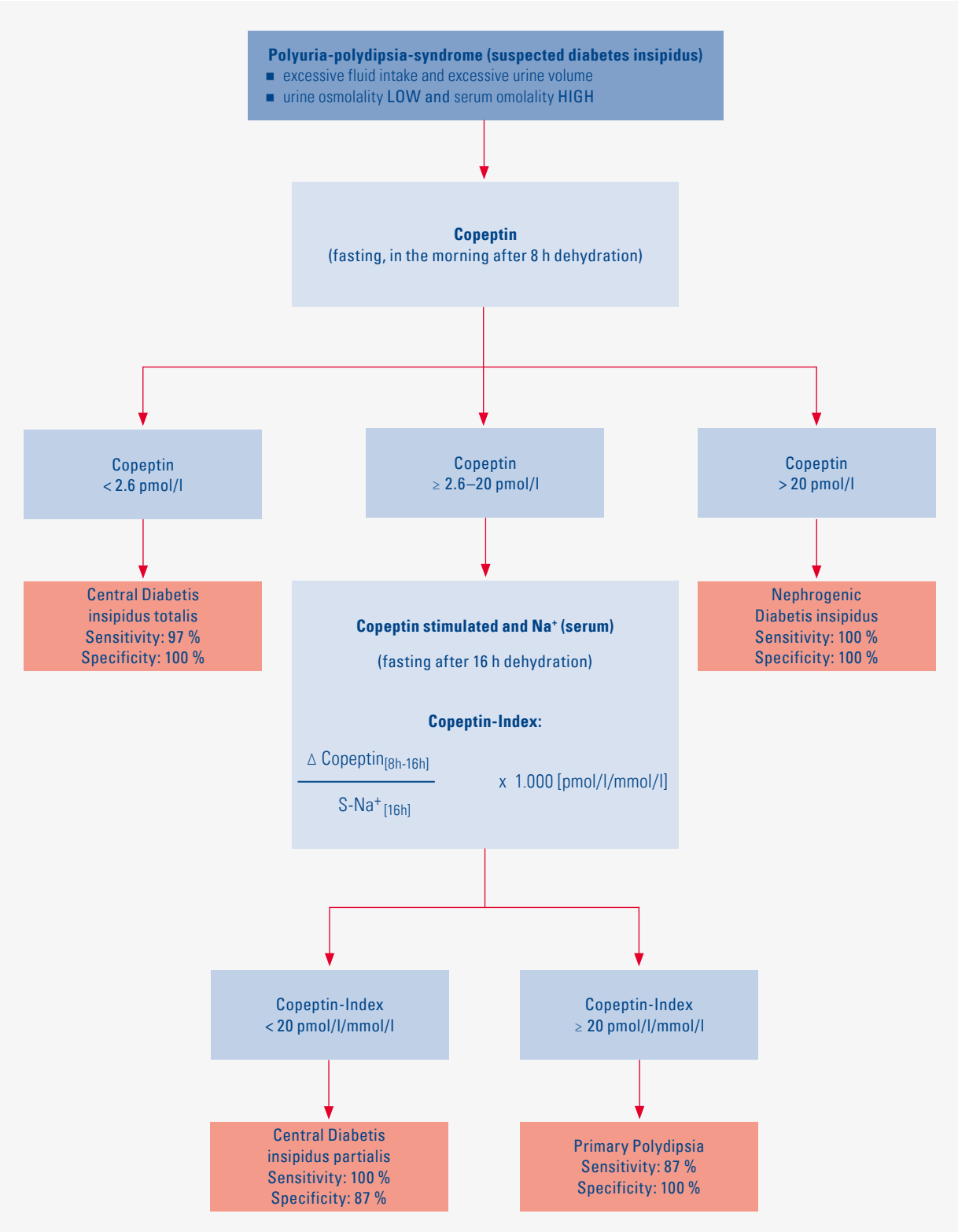
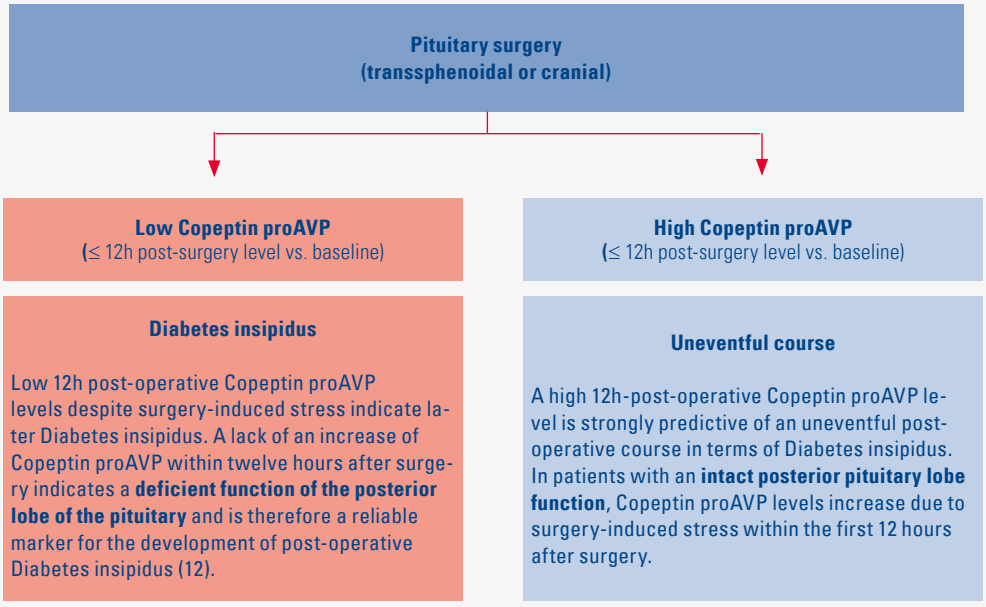


Fig. 3:
Alternate differential diagnostic decision tree for polyuria-polydipsia syndrome on suspicion of diabetis insipidus with Copeptin [9]

Pituitary surgery: easy monitoring for vasopressin deficiency

Pituitary tumors can cause various hormone deficiencies and water metabolism disorders due to their unique site. Remarkably, after pituitary surgery, diabetes insipidus is observed in 18,5 % of patients and hyponatremia in 9 % – 24 %. Therefore, during recovery from pituitary surgery, patients should be closely monitored for possible hormone deficiencies including lack of vasopressin during the postoperative recovery phase (figure 4) (11).



	Copeptin proAVP values	
	Pre-operative (pM, median [IQR])	Post-operative (pM, median [IQR])
Uneventful course (n =155)	3,92 [2,5 - 6,5]	10,8 [5,2 - 30,4]
Diabetes insipidus (n =50)	2,9 [1,9 - 4,7]	2,9 [1,9 - 7,9]
	p=0,04	p<0,001

Fig. 4:
Copeptin proAVP measurements at different time points in patients before (0 hours) and after pituitary surgery.

Traumatic brain injury: reliable follow-up for hypopituitarism

Neurohypophyseal dysfunction is common following moderate to severe brain injury. Diabetes insipidus can occur in up to 26 % of traumatic brain injury victims in the acute phase, as can hyponatremia as a consequence of SIADH (Syndrome of Inappropiate Antidiuretic Hormone Secretion) (13). Recent pilot studies suggest a potential value of Copeptin in following patients with traumatic brain injury.

Sample requirement

- 1 ml serum **frozen**
- method: TRACE

Reference range

Osmolality (mosmol/kg)	Copeptin (pmol/l)
270 – 280	0.81 – 11.6
281 – 285	1.0 – 13.7
286 – 290	1.5 – 15.3
291 – 295	2.3 – 24.5
296 – 300	2.4 – 28.2

Tab. 1

In the differential diagnosis of diabetes insipidus, after 8 hours' water deprivation (fasting blood sample collected in the morning) Copeptin can be evaluated as follows (figure 3):

Copeptin < 2.6 pmol/l: (Sensitivity: 95 % Specificity: 100 %)	Central diabetes insipidus totalis
Copeptin 2.6–20 pmol/l:	Further investigation needed (see Fig. 3)
Copeptin > 20 pmol/l: (Sensitivity: 100 % Specificity: 100 %)	Nephrogenic diabetes insipidus

Tab. 2

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