Diabetes Insipidus
An Update

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KEYWORDS

• Polyuria polydipsia syndrome • Diabetes insipidus • Primary polydipsia

KEY POINTS

- There are 3 main types of polyuria polydipsia syndrome, namely, central diabetes insipidus, nephrogenic diabetes insipidus and primary polydipsia.
- In addition, gestational diabetes insipidus can occur owing to increased arginine vasopressin metabolism during pregnancy.
- Copeptin, the C-terminal segment of the arginine vasopressin prohormone, is an easy-to-measure arginine vasopressin surrogate.
- Copeptin measurement upon osmotic stimulation with hypertonic saline or upon nonosmotic stimulation improves the differential diagnosis of diabetes insipidus.
- Treatment of central diabetes insipidus has not changed significantly. Desmopressin is the treatment of choice, in oral or nasal form.

INTRODUCTION

Diabetes insipidus is one of the main causes of the polyuria polydipsia syndrome and is characterized by a high hypotonic urinary output of more than 50 mL/kg body weight per 24 hours, accompanied by polydipsia of more than 3 L/d.[1] After exclusion of osmotic diuresis (such as uncontrolled diabetes mellitus), the differential diagnosis of diabetes insipidus involves the distinction between primary forms (with central or renal origin) and secondary forms of polyuria (resulting from primary polydipsia). Central diabetes insipidus, also called hypothalamic or neurogenic diabetes insipidus, results from inadequate secretion and usually deficient synthesis of arginine vasopressin (AVP) in the hypothalamic neurohypophyseal system in response to osmotic stimulation. It is mostly acquired owing to disorders that disrupt the neurohypophysis. Less

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commonly, it is congenital by genetic mutations of the AVP gene.[2] Nephrogenic diabetes insipidus can be congenital owing to mutations in the gene for the AVP V2R or the aquaporin 2 (AQP2) water channel.[3] More common, however, it presents as an adverse effect of certain drugs, most prominently lithium, or owing to electrolyte disorders, that is, hypercalcemia or hypokalemia. Last, primary polydipsia is characterized by excessive fluid intake leading to polyuria in the presence of intact AVP secretion and appropriate antidiuretic renal response. The chronic polydipsia eventually leads to a decreased concentration ability of the kidneys—the so-called wash out phenomenon—which makes it difficult to differentiate it from diabetes insipidus.[4]

Differentiation between the 3 mentioned entities is important because the treatment strategies vary and application of the wrong treatment can be dangerous.[5] Reliable differentiation is, however, often difficult to achieve,[6] especially in patients with primary polydipsia or partial, mild forms of diabetes insipidus.[1,7]

This review describes the different types and etiologies of diabetes insipidus and then focuses on new procedures in the differential diagnosis of diabetes insipidus. Treatment is discussed briefly as well.

POLYURIA POLYDIPSIA SYNDROME

Diabetes insipidus is a rare disease with a prevalence of approximately 1:25,000.[8] The disorder can manifest at any age, and the prevalence is similar among males and females. The clinical manifestation of diabetes insipidus, characterized by excessive excretion of large volumes of diluted urine, is caused by a decrease in the secretion or action of AVP. There are 3 main types of polyuria polydipsia, which are characterized by a different defect. In addition, gestational diabetes insipidus can occur owing to increased AVP metabolism during pregnancy (**Fig. 1**, **Table 1**).

The most common type is central diabetes insipidus, and is caused by inadequate AVP production and secretion from the posterior pituitary in response to osmotic stimulation. In most cases, this effect is due to destruction of the neurohypophysis by a variety of acquired causes, for example, trauma, surgery, vascular or granulomatous etiologies (see **Table 1**). It can also be of congenital origin, in which case it is most often owing to an autosomal dominant AVP gene mutation.[9]

A second variant of diabetes insipidus is caused by decreased renal sensitivity to the antidiuretic effect of physiologic levels of AVP.[3] This AVP insensitivity leads to a deficiency of AQP-mediated water reabsorption in the collecting duct. This nephrogenic variant of the diabetes insipidus can be due to mutations of the key proteins AVP V2 receptor and AQP2; however, it can also be secondary to drug exposure (especially lithium), infiltrating lesions of the kidneys or vascular disorders, among others (see **Table 1**).

A third mechanism of the clinical syndrome is due to physiologic suppression of AVP secretion by excessive, osmotically independent fluid intake plus loss of the renal concentration ability owing to the washout phenomenon described elsewhere in this article.[4] This type is referred to as primary polydipsia to distinguish it from the secondary polydipsia that occurs in response to water loss in other types of diabetes insipidus. In addition to psychiatric patients and health enthusiasts, there is a small subgroup of patients with primary polydipsia commonly referred to as having dipsogenic diabetes insipidus, in which polydipsia seems to be due to an abnormally low thirst threshold.[10]

A final type of defect, gestational diabetes insipidus, is caused by an increased degradation of AVP by the placenta enzyme vasopressinase,[11,12] thus presenting similar to the abnormalities in central diabetes insipidus. In some cases, patients

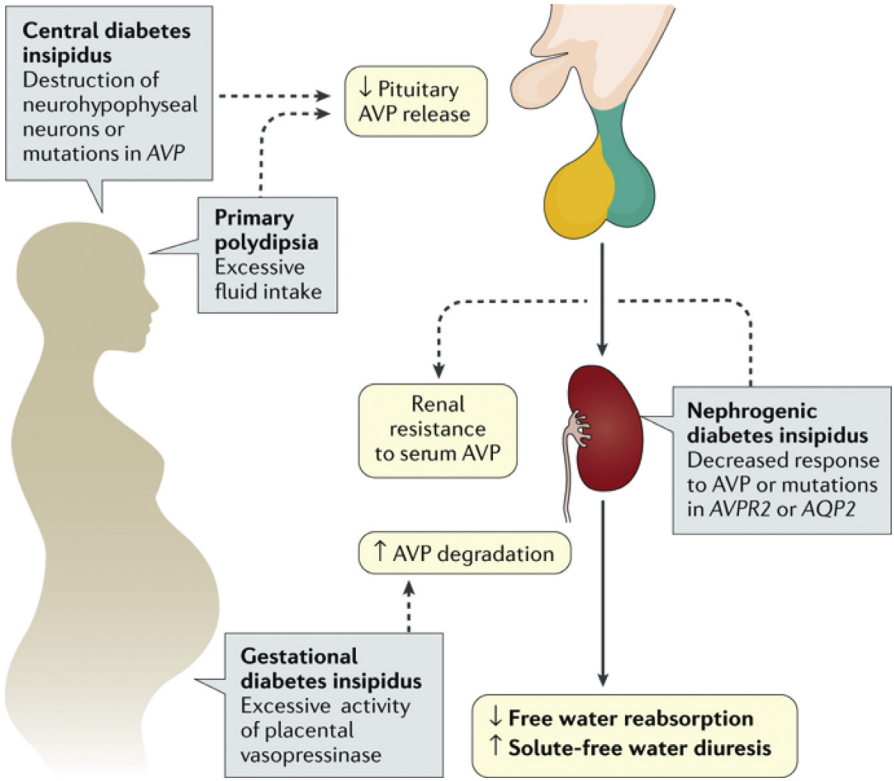

Fig. 1. Different etiologies of polyuria polydipsia syndrome. (*From* Christ-Crain M, Bichet DG, Fenske WK, et al. Diabetes insipidus. Nat Rev Dis Primers. 2019; 8;5(1):54; with permission.)

may be predisposed to its development by preexisting, subclinical deficiency in AVP.[13,14] All etiologies are summarized in **Table 1** and in **Fig. 1**.

DIABETES INSIPIDUS: AN UPDATE ON DIAGNOSIS

Clinical Manifestations

The lead symptoms of diabetes insipidus are increased thirst, polyuria, and polydipsia, which are not necessarily different in their specific manifestation between diabetes insipidus and primary polydipsia.[15] Patients with central diabetes insipidus more often describe nocturia and a sudden onset of symptoms. This results from the fact that urinary concentration can often be maintained fairly well until the residual neuronal capacity of the hypothalamus to synthesize AVP decreases to less than 10% to 15% of normal, after which urine output increases dramatically.

Patients with diabetes insipidus, especially those with underlying osmoreceptor defect syndromes, can manifest with varying degrees of dehydration and hyperosmolality, if renal water losses cannot be fully compensated by fluid intake. Resulting symptoms can be divided into those produced by dehydration, which are largely cardiovascular (including hypotension, acute tubular necrosis secondary to renal hypoperfusion, and shock)[16,17] and those caused by hyperosmolality. The latter are mainly neurologic and reflect the degree of brain dehydration as a result of osmotic

Table 1
Etiology of polyuria polydipsia syndrome

Type of Hypotonic Polyuria	Basic Defect	Causes
Central diabetes insipidus	Deficiency in AVP synthesis or secretion	Acquired Trauma (surgery, deceleration injury) Neoplastic (craniopharyngioma, meningioma, germinoma, metastases) Vascular (cerebral/hypothalamic hemorrhage, infarction or ligation of anterior communicating artery aneurysm) Granulomatous (histiocytosis, sarcoidosis) Infectious (meningitis, encephalitis, tuberculosis) Inflammatory/autoimmune (lymphocytic infundibuloneurohypophysitis, IgG4 neurohypophysitis) Drug/toxin induced Osmoreceptor dysfunction (adipsic diabetes insipidus) Others (hydrocephalus, ventricular/suprasellar cyst, trauma, degenerative disease) Idiopathic Congenital Autosomal dominant: AVP gene mutation Autosomal recessive: Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) X-linked recessive
Nephrogenic diabetes insipidus	Reduced renal sensitivity to antidiuretic effect of physiologic AVP levels	Acquired Drug exposure (lithium, demeclocyclin, cisplatin, etc) Hypercalcemia, hypokalemia Infiltrating lesions (sarcoidosis, amyloidosis, multiple myeloma, etc) Vascular disorders (sickle cell anemia) Mechanical (polycystic kidney disease, urethral obstruction) Congenital X-linked *AVPR2* gene mutations Autosomal recessive or dominant *AQP2* gene mutations

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Table 1
(continued)

Type of Hypotonic Polyuria	Basic Defect	Causes
Primary polydipsia	Excessive osmotically unregulated fluid intake	Dipsogenic (downward resetting of the thirst threshold; idiopathic or similar lesions as with central diabetes insipidus) Psychosis intermittent hyponatremia polydipsia (psychosis, intermittent hyponatremia, and polydipsia syndrome) Compulsive water drinking Health enthusiasts
Gestational diabetes insipidus	Increased enzymatic metabolism of circulating AVP hormone	Increased AVP metabolism Pregnancy

water shifts from the intracellular compartment. Manifestations may range from nonspecific symptoms such as irritability and cognitive dysfunction to more severe manifestations such as disorientation, reduced consciousness, seizure, coma, focal neurologic deficits, and cerebral infarction.[16,18]

Radiologic Findings

Sometimes useful information in the differential diagnosis of diabetes insipidus may derive from unenhanced brain MRI via assessment of the posterior pituitary and the pituitary stalk. An area of hyperintensity, often referred to as the pituitary "bright spot," is normally observed in the posterior part of the sella turcica in sagittal views on T1-weighted images,[19] and is thought to result from the T1-shortening effects of stored AVP in neurosecretory granules of the posterior lobe of the pituitary.[20] Although earlier small-scale studies demonstrated the presence of the bright spot in normal subjects and its absence in patients with central diabetes insipidus,[21] subsequent larger studies reported an age-related absence of the bright spot in up to 52% to 100% of normal subjects.[22] Conversely, individual cases with persistent bright spot have been reported in patients with central diabetes insipidus,[23,24] possibly owing to an early stage of disease or a reflection of oxytocin stores rather than AVP. In nephrogenic diabetes insipidus, the bright spot has been reported to be absent in some patients, but present in others.[25] A recent large prospective observation of 92 patients with polyuria polydipsia syndrome receiving brain MRI revealed absence of the bright spot in 70% of patients with central diabetes insipidus but also in 39% of patients with primary polydipsia.[15] Consequently, the presence or absence of the bright spot on MRI seems not to be qualified as a diagnostic test in patients with diabetes insipidus.

A similar conclusion seems to apply to the assessment of the pituitary stalk, whose enlargement beyond 2 to 3 mm is generally considered to be pathognomonic,[26] but is not necessarily specific for idiopathic central diabetes insipidus.[15,27] The situation is quite different if scans reveal thickening of the stalk with an absence of the bright spot; in this case, a diligent search for neoplastic or infiltrative lesions of the hypothalamus or pituitary gland is indicated.[28]

Tests for Differential Diagnosis of Diabetes Insipidus

Differentiation between the 3 main entities (ie, central diabetes insipidus, nephrogenic diabetes insipidus, and primary polydipsia) is important because the treatment strategies vary and application of the wrong treatment can be dangerous.[5] However, reliable differentiation has proved difficult in the past,[6] because many available tests are unsatisfactory[29] and often result in false diagnoses, especially in patients with primary polydipsia or partial, mild forms of diabetes insipidus.[1,7]

The water deprivation test

The accepted gold standard for many years for differential diagnosis of polyuria polydipsia syndrome was the indirect water deprivation test. This test is based on the concept that AVP activity is indirectly assessed by measurement of the urine concentration capacity during a prolonged period of dehydration, and again after a subsequent injection of an exogenous synthetic AVP variant (desmopressin).[30–32] Interpretation of the test results is based on recommendations from Miller and colleagues.[33] Nephrogenic diabetes insipidus is diagnosed if urinary osmolality remains below 300 mOsm/kg with water deprivation and does not increase by more than 50% after exogenous synthetic AVP injection. If the respective increase upon exogenous synthetic AVP is more than 50%, complete diabetes insipidus is diagnosed. In partial central diabetes insipidus and primary polydipsia, urinary concentration increases to 300 to 800 mOsm/kg, with an increase upon desmopressin of more than 9% (in partial central diabetes insipidus) and less than 9% (in primary polydipsia).

However, these criteria from Miller and colleagues are based on data from only 36 patients, showing a wide overlap in urinary osmolalities. Furthermore, the diagnostic criteria for this test are derived from a single study with post hoc assessment[33] and have not been prospectively validated on a larger scale (for details see[5]). Consequently, the indirect water deprivation test has been shown to have considerable diagnostic limitations, with an overall diagnostic accuracy of 70%, and an accuracy of only 41% in patients with primary polydipsia.[7] These findings have been confirmed in a recent large prospective observation on 156 patients with polyuria polydipsia syndrome.[15]

There are several reasons for the disappointing diagnostic outcome of the indirect water deprivation test. First, chronic polyuria itself can affect renal concentration capacity through renal washout or downregulation of expression of AQP2 water channels in the kidney.[4] This process may lead to a reduced renal response to osmotic stimulation or to exogenous desmopressin[4] in different forms of chronic polyuria.[33] Second, in patients with a deficiency of AVP, urine concentration can be higher than expected,[34,35] especially in patients with impaired glomerular function,[29,36,37] or as a result of a compensatory increase in *AVPR2* gene expression in chronic central diabetes insipidus.[38] Finally, patients with acquired nephrogenic diabetes insipidus often exhibit only a partial resistance to AVP leading to a higher than expected increase in urine osmolality upon exogeneous desmopressin administration.

Arginine vasopressin measurement

To overcome these limitations of the indirect water deprivation test, direct measurement of AVP has been proposed to improve the differential diagnosis of polyuria polydipsia syndrome. Indeed, first data published in 1981[39] reported that patients with central diabetes insipidus showed AVP levels of less than a calculated normal area (defining the normal relationship between plasma osmolality and AVP levels), whereas patients with nephrogenic diabetes insipidus showed levels above the normal area, and patients with primary polydipsia demonstrated concentrations within the normal

range. However, despite these promising first results, AVP measurement failed to enter routine clinical use. The main reason for this are the technical limitations of the AVP assay resulting in a high preanalytical instability.[35,40,41] Second, the results of studies using commercially available AVP assays have been disappointing, with a diagnostic accuracy of only 38% and particularly poor differentiation between partial central diabetes insipidus and primary polydipsia.[5,7] Third, an accurate definition of the normal physiologic area defining the relationship between plasma AVP and osmolality is still lacking, especially for commercially available assays.[39,42,43] This, however, is a crucial prerequisite for the identification of inadequate AVP secretion in patients suspected of diabetes insipidus.[7]

Copeptin-based new diagnostic algorithms

Copeptin, the C-terminal segment of the AVP prohormone, is an easy-to-measure AVP surrogate with high ex vivo stability.[41] Despite a possible involvement in the folding of the AVP precursor,[44,45] no physiologic role for copeptin has yet been found. However, copeptin shows a strong correlation with AVP and plasma osmolality, the latter correlation being even stronger than for AVP.[46] The observation that copeptin reflects osmosensitive circulating AVP concentrations makes copeptin a promising biomarker for the differential diagnosis of polyuria polydipsia syndrome.

Two studies have shown that a basal copeptin level greater than 21.4 pmol/L without prior thirsting unequivocally identifies nephrogenic diabetes insipidus, rendering a further water deprivation unnecessary in these patients.[7,47] However, for the more challenging differentiation between patients with primary polydipsia and central diabetes insipidus osmotically stimulated copeptin values are needed because baseline levels show a large overlap in those patient groups.[47] The use of osmotically stimulated copeptin levels as a diagnostic tool for diabetes insipidus has recently been confirmed in the so far largest study including 156 patients with diabetes insipidus or primary polydipsia.[15] Osmotic stimulation was achieved using a body weight–adapted hypertonic (3%) saline infusion aimed at a plasma sodium level of 150 mmol/L or greater, at which time copeptin was measured. In a head-to-head comparison, osmotically stimulated copeptin at a cut-off level of greater than 4.9 pmol/L showed a greater diagnostic accuracy of 97% (93% sensitivity and 100% specificity) to distinguish patients with primary polydipsia from patients with central diabetes insipidus compared with the classical water deprivation test with an accuracy of 77% (86% sensitivity and 70% specificity).[15] Copeptin taken at the end of the water deprivation test did not improve its diagnostic accuracy. This finding is best explained by the insufficient osmotic stimulus achieved by water deprivation alone.[15] The diagnostic accuracy of the 2 tests in comparison is shown in **Fig. 2**.

In addition to its superior diagnostic accuracy, the hypertonic saline stimulation test comes with the advantage that it can be performed in the out-patient clinic, whereas in most countries patients have to be hospitalized for the water deprivation test. Also, despite the adverse symptoms associated with osmotic stimulation, patients seem to prefer it over the water deprivation test.[15]

According to these data, copeptin can be used as a reliable biomarker to discriminate between different forms of the polyuria polydipsia syndrome, therefore the osmotic stimulated copeptin levels will probably replace the classical water deprivation test in the future. However, it has to be noted that the hypertonic saline infusion test requires close monitoring of sodium levels to ascertain a diagnostically meaningful increase of plasma sodium within the hyperosmotic range,[48,49] while preventing a marked increase.

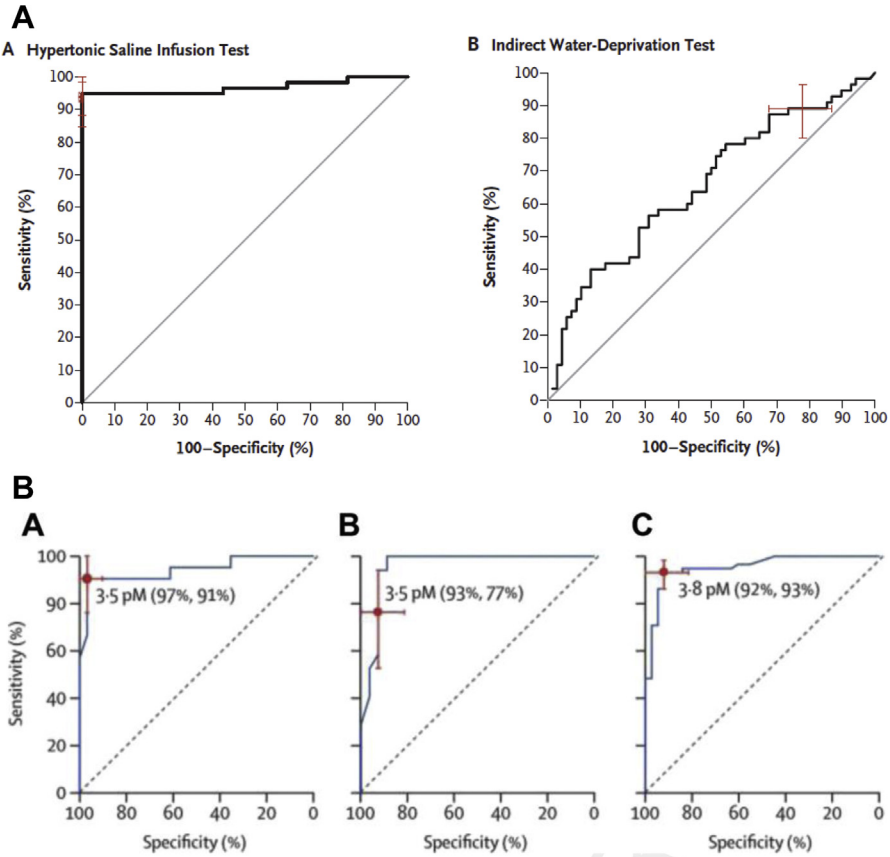

Fig. 2. (*A*) ROC analysis of hypertonic saline test plus copeptin measurement (panel A) as compared to the indirect water deprivation test (panel B). (*B*) ROC analysis of arginine-stimulated copeptin level (panel A-C). (panel A) ROC for the derivation cohort, (panel B) validation cohort, (panel C) whole cohort. ([*A*] *From* 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; with permission; and [*B*] 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(10198):587-95; with permission.)

An easier approach to stimulate copeptin—without inducing high sodium levels—is via arginine infusion. Indeed, arginine infusion, which has widely been used to stimulate growth hormone and therefore to test for growth hormone deficiency,[50] is also a potent nonosmotic stimulus of the posterior pituitary gland. Arginine-stimulated copeptin values were evaluated in a prospective diagnostic study with 98 patients with central diabetes insipidus or primary polydipsia.[51] A copeptin cutoff of 3.8 pmol/L at 60 minutes after arginine infusion had an accuracy of 93% (sensitivity 93%, specificity 92%) to diagnose diabetes insipidus[51] (see **Fig. 2**). The test was safe and well-tolerated, although nausea was a frequently reported symptom. Importantly, other adverse effects such as vertigo, headache, or malaise (previously described in ≥70% of patients during the hypertonic saline infusion test)[15] were negligible during arginine stimulation. Further advantages of the arginine test over the hypertonic saline infusion test and the water deprivation test are the shorter test duration

(a single copeptin measurement after 60 minutes is sufficient) and the improved feasibility without the need for sodium monitoring.

Accordingly, this proof-of-concept study offers the promise of a simple and convenient test that may become the standard diagnostic approach for diabetes insipidus. A definitive head-to-head study comparing the diagnostic accuracy of hypertonic saline-stimulated versus arginine-stimulated copeptin measurement is currently ongoing (NCT03572166). Pending those results, we suggest a stepwise approach: a diagnostic workflow favoring copeptin as a critical diagnostic marker in the differentiation of polyuria polydipsia syndrome, as shown in **Fig. 3**.

Copeptin has also been evaluated as a predictive marker for the development of diabetes insipidus in the setting of sellar region operations. The manipulation or damage of the pituitary gland during surgery may lead to postoperative diabetes insipidus and severe hypernatremia in the early postoperative period if fluid is not adequately replenished. A prospective multicenter study including 205 patients undergoing pituitary surgery showed that patients who did not exhibit a pronounced stress-induced copeptin increase after surgery (reflecting a damaged neurohypophysis) were at risk for postoperative central diabetes insipidus.[52] In this cohort, 50 patients (24%) developed postoperative central diabetes insipidus, which was predicted by a postoperative (measured within the first 12 hours after surgery) copeptin value of less than 2.5 pmol/L with a high specificity of 97% (positive predictive value of 81%). In contrast, a high postoperative copeptin value of greater than 30 pmol/L was predictive of an uneventful postoperative course and excluded the development of central diabetes insipidus with a negative predictive value of 95% and a sensitivity of 94%.

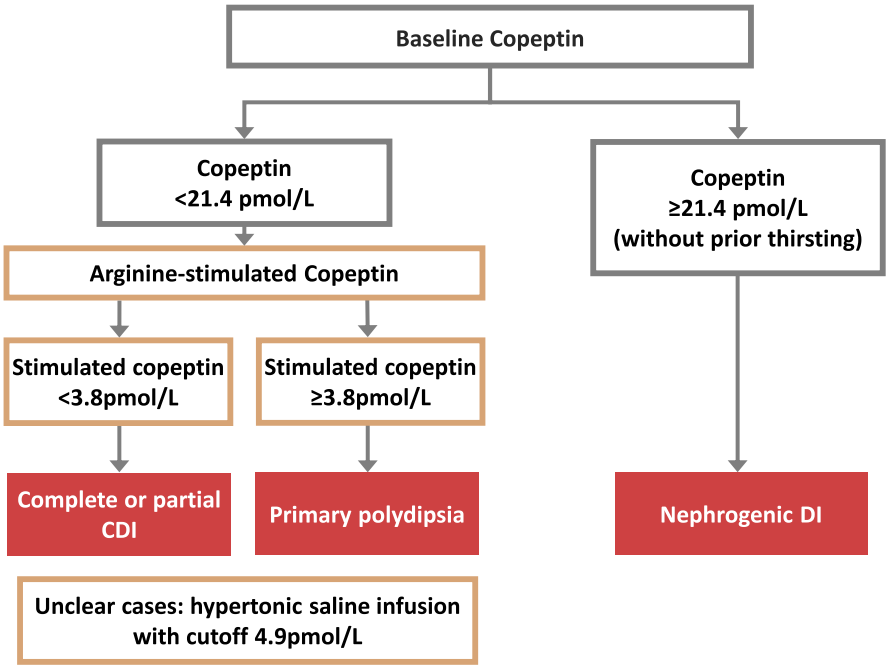

Fig. 3. Suggested copeptin-based 2-step algorithm in the differential diagnosis of polyuria polydipsia syndrome.

A recent smaller study evaluating 66 patients undergoing pituitary surgery suggested using copeptin values 1 hour after extubation to predict central diabetes insipidus.[53] In this study, a copeptin value of less than or equal to 12.8 pmol/L indicated patients at risk for central diabetes insipidus. Moreover, a copeptin level of 4.2 pmol/L or greater excluded permanent forms. Although the reliability of their proposed cut offs is limited by the small number of affected patients (n = 8), their results confirmed postoperative copeptin measurements as a useful tool for risk stratification of the development of postoperative central diabetes insipidus. Additionally, the extent of stress-induced AVP/copeptin release at this early time point after extubation may distinguish between transient and permanent forms of diabetes insipidus.

DIABETES INSIPIDUS: AN UPDATE ON MANAGEMENT

In contrast with the diagnostic evaluation, treatment of diabetes insipidus did not significantly change over the last decades. Therefore, we briefly summarize the current treatment options for central and nephrogenic diabetes insipidus.

Untreated central and nephrogenic diabetes insipidus may lead to hyperosmolar dehydration. The general goals of treatment of all forms of diabetes insipidus are therefore a correction of any preexisting water deficits and a reduction in ongoing excessive urinary water losses (for details please see[54]).

Specific replacement therapy for central diabetes insipidus treatment is usually straightforward and primarily aims at ameliorating symptoms (polyuria and polydipsia) by replacing antidiuretic hormone. Desmopressin, an AVP analogue, is the preferred drug for almost all patients. To avoid the risk of hyponatremia, patients should be instructed to avoid excessive fluid intake and it is suggested to measure the serum sodium within the first days after the initiation of desmopressin therapy. Patients should be educated about hyponatremia symptoms like nausea, vomiting, headache, lethargy, or seizures. Once a stable dose of desmopressin is achieved, annual monitoring of the serum sodium should be performed.

Desmopressin is dosed empirically. The initial aim of therapy is to reduce nocturia and therefore the first dose is usually given at bedtime and, if needed, a daytime dose is added. In most cases, diabetes insipidus is permanent and therefore requires lifelong treatment. However, after neurosurgery, diabetes insipidus is mostly only transient.[55] Therefore, patients with diabetes insipidus after trans-sphenoidal surgery should not receive a fixed dose of desmopressin, but the degree of polyuria should be monitored and if polyuria becomes less pronounced or ceases, desmopressin can be tapered or withdrawn. If diabetes insipidus is still present 2 weeks after surgery, permanent diabetes insipidus becomes more likely. Desmopressin can be administered intranasally, orally, subcutaneously, or intravenously (**Table 2**).

Usually, starting with an intranasal preparation is recommended because not all patients respond to oral therapy. For the intranasal preparation, an initial dose of 10 μg at bedtime can be titrated upward in 10 μg increments. The usual daily maintenance

Table 2
Different forms and administrations of desmopressin treatment

Application	IV/SC/IM	Intranasal	Per Os	Sublingual
Concentration	4 μg/mL	0.1 mg/mL 10 μg/dosage	100/200 μg tablets	60/120/240 μg tablets
Starting dosage	1 μg	10 μg	50 μg	60 μg

dose is 10 to 20 μg once or twice per day. For the oral preparation, the initial dose is 0.05 mg at bedtime with titration upward until 0.10 mg to 0.80 mg (maximum of 1.2 mg) in divided doses. Because the oral dose cannot be precisely predicted from a previous nasal dose, transfer of patients from nasal to oral therapy usually requires some dose retitration.

For intravenous administration, 1 to 2 μg of desmopressin acetate may be given over 2 minutes; the duration of action is 12 hours or more.

A special challenge in treatment are patients with osmoreceptor dysfunction. The long-term management of these patients requires measures to prevent dehydration and at the same time to prevent water intoxication. Because loss of thirst perception mostly cannot be cured, the focus of management is based on education of the patient about the importance of regulating their fluid intake according to their hydration status.[56] This monitoring can be accomplished most efficaciously by a fixed daily fluid intake regardless of the patient's thirst, which can be adjusted in response to changes in body weight. If the patient has polyuria, desmopressin should also be prescribed. The success of the fluid prescription should be monitored periodically by measuring serum sodium concentration. If treated accordingly, central diabetes insipidus is associated with a fairly normal quality of life, particularly when oral or nasal desmopressin is prescribed.

Nephrogenic diabetes insipidus is more difficult to treat because these patients have at least partial resistance to AVP agents. Response to (sub)maximal doses of desmopressin is, however, possible in some patients. Of course, the underlying disorder (eg, hypercalcemia) should be corrected if possible.

Patients should be instructed to follow a low-sodium diet, leading to modest hypovolemia, which stimulates isotonic proximal tubular reabsorption and thereby reduces solute delivery to the distal parts of the nephron.[3] Thiazide diuretics are sometimes efficient owing to induced natriuresis, mainly if combined with a low sodium diet. Nonsteroidal anti-inflammatory agents can also be used because they block prostaglandin synthesis, thereby increasing non–AVP-dependent water reabsorption.

Amiloride is the preferred drug to prevent progression or possibly improve lithium-induced diabetes insipidus in patients in whom lithium is continued. Usually, nephrogenic diabetes insipidus is reversible after lithium withdrawal. However, in some cases it takes several months or years for the full recovery of the renal ability to concentrate urine and very few patients have irreversible nephrogenic diabetes insipidus, even with discontinuation of lithium.

Treatment options for primary polydipsia patients are limited. A stepwise voluntary reduction of fluid intake is the treatment of choice, but often fails owing to the strong thirst perception in those patients.[57] Accordingly, most treatment recommendations aim at the prevention of hyponatremia occurrence. This goal might be achieved through patient education, recommending a balanced diet, and body weight monitoring to avoid water retention. Furthermore, any drugs with dry mouth effects should be avoided whenever possible. Supportive measures such as behavioral therapy or antipsychotics have been evaluated. However, success rates vary and these interventions are best implemented on an individual patient basis.

SUMMARY

In the diagnosis and differential diagnosis of diabetes insipidus, new test methods have shown greater diagnostic accuracy than the classical water deprivation test. These diagnostic algorithms are based on the measurement of copeptin measured

either after osmotic stimulation by hypertonic saline infusion or after nonosmotic stimulation by arginine. A head-to-head study comparing these 2 test methods is currently ongoing.

Treatment of diabetes insipidus has not significantly changed within the last years and involves correction of any preexisting water deficits, if present, and exogeneous desmopressin for patients with central diabetes insipidus, which most often is given as an oral or nasal application. Most important, patients have to be instructed about the risk for hyponatremia.

COMPETING INTERESTS

M. Christ-Crain received speaking honoraria from Thermo Fisher AG, the manufacturer of the copeptin assay.

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