Current State and Future Perspectives in the Diagnosis of Diabetes Insipidus: A Clinical Review

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Context: The differential diagnosis of diabetes insipidus (DI) is often challenging but essential, because treatment may vary substantially. This article analyzes the database and performance of currently used differential diagnostic tests for DI and discusses future perspectives for diagnostic improvement.

Evidence Acquisition: A review of electronic and print data comprising original and review articles retrieved from the PubMed or Cochrane Library database up to January 2012 was conducted. The search term “polyuria polydipsia syndrome” was cross-referenced with underlying forms of disease and associated clinical, diagnostic, and therapeutic MeSH terms. In addition, references from review articles and textbook chapters were screened for papers containing original data. Search results were narrowed to articles containing primary data with a description of criteria for the differential diagnosis of DI.

Evidence Synthesis: Fifteen articles on differential diagnosis of DI were identified, mainly consisting of small series of patients, and mostly covering only part of the differential diagnostic spectrum of DI. Test protocols differed, and prospective validation of diagnostic criteria was consistently missing. Inconsistent data were reported on the diagnostic superiority of direct plasma arginine vasopressin determination over the indirect water deprivation test. Both test methods revealed limitations, especially in the differentiation of disorders with a milder phenotype.

Conclusion: The available data demonstrate limitations of current biochemical tests for the differential diagnosis of DI, potentially leading to incorrect diagnosis and treatment. The newly available assay for copeptin, the C terminus of the vasopressin precursor, holds promise for a higher diagnostic specificity and simplification of the differential diagnostic protocol in DI. (J Clin Endocrinol Metab 97: 3426–3437, 2012)

Diabetes insipidus (DI) belongs to the spectrum of polyuric and polydipsic diseases, a group of hereditary or acquired disorders mainly associated with an inadequate arginine vasopressin (AVP) secretion or renal response to AVP, which clinically results in hypotonic polyuria and a compensatory or underlying polydipsia.

Under physiological conditions, body water and osmotic homeostasis are balanced by a sensitively regulated AVP system essentially depending on two determinants, the serum osmolality and arterial blood volume (1). AVP activates the renal vasopressin-2 receptor (V2R) at the basolateral membrane of the principal cells and increases the tubular fluid permeability via cAMP-induced phosphorylation and insertion of the water channels aquaporin 2 (AQP2) into the apical membrane (2). Thirst serves as an important backup mechanism, becoming indispensible in the moment when pituitary and renal mechanisms fail to maintain body fluid homeostasis. Under these circumstances, intact thirst sensation is essential to restore normal osmolality, but often at the expense of a clinically pronounced polyuria and polydipsia. Differentiating primary polydipsia (PP) from secondary polydipsia is impor-

Abbreviations: AQP2, Aquaporin 2; AVP, arginine vasopressin; CDI, central (or neurogenic) DI; cMRI, cranial magnetic resonance imaging; DI, diabetes insipidus; NDI, nephrogenic DI; PP, primary polydipsia; V2R, vasopressin-2 receptor.
tant because incorrect treatment may lead to serious complications. Although simple dehydration should theoretically enable the differentiation of both disorders, this approach often fails, especially in mild forms of DI (3).

The purpose of this review is to provide a comprehensive discussion of the available database on the differential diagnosis of DI to better appreciate the diagnostic evidence and strengths, but also the limitations and pitfalls of the currently available test concepts.

Clinical Spectrum of the Underlying Disorders

Central diabetes insipidus

Central or neurogenic DI (CDI) is the most common form of polyuric and polydipsic disorder, which occurs mainly due to lesions of the neurohypophysis or the hypothalamic median eminence resulting in deficient synthesis and/or release of AVP. A number of acquired and congenital disorders may cause CDI (Table 1) (4–6) with variable clinical manifestation, depending on the extent of neuronal destruction. Usually 80 to 90% of the magnocellular neurones in the hypothalamus need to be damaged before symptoms of DI arise (7).

Acquired CDI mostly results from transsphenoidal surgery or head trauma. Twenty to 30% of pituitary surgeries lead to transient CDI, and 2–10% lead to permanent disease (8, 9), with a risk of postoperative neuronal damage depending on the height of hypothalamic-hypophyseal tract destruction; sections above the median eminence cause a permanent form of disease, whereas sections below the median eminence produce only transient CDI (10).

CDI due to pituitary adenomas is extremely rare (11, 12), even when associated with complete anterior pituitary insufficiency (13). Similarly rare, but important to consider, is an autoimmune destruction of the neurohypophysis caused by lymphocytic infundibuloneurohypophysitis, an entity presenting with a thickened pituitary stalk and enlargement of the neurohypophysis in cranial magnetic resonance imaging (cMRI) (14–17), which in individual cases may spontaneously go into remission (6, 14, 17). This autoimmune process has also been described in a subset of patients initially classified as idiopathic CDI (14). But idiopathic CDI, accounting for about 25% of disease in adulthood, provides no clinical evidence of injury or diseases that could be linked to DI, and cMRI generally reveals no abnormality other than the absence of the posterior pituitary bright spot and sometimes varying degrees of thickening of the pituitary stalk (6).

Much more rare are the congenital forms of CDI (Table 1), mostly presenting with an autosomal dominant mode of inheritance (18–20), and only very infrequently due to an autosomal recessive (21–23) or X-linked recessive inheritance (24). Underlying mutations, located in the coding region of the AVP-neurophysin precursor gene mediate the generation of an abnormal precursor protein, which accumulates within the neuron and causes cell apoptosis (25). Therefore, congenital CDI typically develops months to years after birth and then gradually progresses (26, 27). Only rare cases of congenital CDI were reported, which later went into remission (28, 29) without evidence for recovered AVP release (30).

Osmoreceptor dysfunction

Different lesions in the anterior hypothalamus near the third ventricle may entail a dysfunction of the osmoreceptors resulting in an impaired AVP responsivity and thirst sensation (Table 1) (31, 32). Patients manifest with dehydration and hypernatremia, sometimes resulting in serious
cardiovascular complications like hypotension, renal failure, and hypovolemic shock (33). The severity of the neurological signs is closely related to the degree of hypertonicity, ranging from irritability to disorientation, seizures, and coma (34). Importantly, patients can still demonstrate a physiological antidiuretic response to baroreceptor-mediated (35) and other non-osmotic stimuli of AVP release (36, 37).

**Nephrogenic diabetes insipidus**

Nephrogenic DI (NDI) results from renal resistance to the antidiuretic action of AVP, which may also be due to acquired or inherited conditions (Table 1).

The acquired form of NDI is much more common than the congenital form, but it is rarely severe. The ability to elaborate a hypertonic urine is usually preserved, despite the impairment of the maximal concentrating ability of the nephron. Therefore, the symptoms of disease are usually more moderate with a polyuria and polydipsia seldom above 3 to 4 liters/d. Lithium therapy poses the most frequent cause of acquired NDI (38), involving about 10–20% of patients treated long term (39). Even at therapeutic concentrations, lithium may interfere with the cAMP system (40, 41), leading to decreased renal AQP2 expression (42) with subsequent polyuria and tubular acidosis (40, 43, 44). This defect in AQP2 is slow to correct (45, 46), and in some cases may even persist when associated with glomerular or tubulointerstitial nephropathy (47).

Also, electrolyte disorders like hypokalemia or hypercalcemia may involve NDI, probably due to a temporary down-regulation of AQP2 expression (45, 48, 49). But the manifestation is reversible once electrolytes are corrected. Almost 90% of the more infrequent congenital NDI is inherited in an X-linked recessive manner due to mutations in the V2R gene. Only 10% of congenital diseases are due to autosomal mutations in the AQP2 gene (50). More than 200 putative disease-causing mutations within the V2R gene have been described (51), and functional characterization of some of these mutant receptors revealed reduced binding affinity for AVP (type 1), defective intracellular trafficking (type 2), or reduced receptor transcription (type 3) (50). The genetic form normally presents from birth with basal serum sodium levels being either normal or elevated if fluid administration is also impaired.

**Primary polydipsia**

PP differs from the other causes of DI in that it does not arise from a deficient AVP secretion or activity, but rather results from an excessive fluid intake practiced over an extended period of time (52, 53). PP comprises subjects with a defective thirst mechanism or increased thirst sen-

**Gestational diabetes insipidus**

For the sake of completeness, the gestational form of DI should also be mentioned. The manifestation is triggered by the degradation of AVP by the placental enzyme cysteine aminopeptidase (59–61), although the hormone levels are often normal (62), suggesting that pregnancy unMASKs a subtle underlying deficiency of AVP (59, 63). Although spontaneous remission of gestational DI normally occurs within 2 to 3 wk postpartum, diagnostic evaluation for possible underlying disorders should be considered (Table 1).

**Differential Diagnosis**

Once hypotonic polyuria has been confirmed, patient history and clinical presentation can provide useful diagnostic clues. But very often, clinical data are of limited help (64) because patients with a preserved thirst mechanism do biochemically not differ significantly. And although the assessment of the integrity of the neurohypophyseal system may be conceptually simple and should theoretically allow a straightforward diagnostic differentiation of DI, interpretational difficulties often arise (65) and not seldom lead to misclassification (64, 66, 67) with a high risk of inappropriate therapy. Therefore, a reliable and generally applicable diagnostic approach to suspected DI is extremely important (3, 68, 69).

To better understand and characterize the limitations and pitfalls of current diagnostic test standards, we per-
formed an extensive literature review, incorporating electronic and manual components with the search term “polyuria polydipsia syndrome” and its underlying diseases. The electronic search was conducted using the PubMed and the Cochrane Library database (up to January 2012) with the following MeSH terms: “diagnosis of polyuria/polydipsia/diabetes insipidus/(posterior) pituitary disease/hypopituitarism”; “psychogenic polydipsia”; “compulsive water drinking”; “water deprivation test”; “hypertonic saline infusion test”; “impaired urinary concentration”; “desmopressin”; and “vasopressin.” In addition, the scientific work of individual authors with exceptional activity in this field (including G. L. Robertson, J. G. Verbalis, D. G. Bichet, P. H. Baylis, and C. J. Thompson) was analyzed separately. Data and references from major textbooks (70–74) were also included in the analysis. Fifteen original articles dealing with the evaluation of differential diagnostic test concepts in DI were retrieved. Design, endpoints, and main findings of these studies are chronologically summarized in Table 2, and the diagnostic key issues in differentiation of DI are discussed in the following paragraphs against this database.

The urinary concentration test as an indirect measure of AVP activity

Our current diagnostic test concepts of DI date back to animal studies from Gilman and Goodman (75, 76) in the 1930s, which first demonstrated that osmotic stimulation by dehydration (75, 76) or hypertonic saline infusion (77) induces an antidiuretic urinary response that is not observed in hypophysectomized dogs (78).

Hickey and Hare (79) first applied these findings to man, demonstrating that patients with CDI (n = 2) have a higher tubular chloride reabsorption and a higher water diuresis during osmotic stimulation than patients with PP (n = 1) (Table 2). Carter and Robbins (80) equally reported a much lower reduction in urine flow in subjects with CDI (n = 8) when compared with PP (n = 3) (Table 2). Both studies, therefore, suggest that the urinary concentration capacity may provide useful information in the diagnostic differentiation of DI. But the urinary concentration mechanism may be disturbed under certain circumstances (e.g., in states of anterior pituitary insufficiency, overhydration, or reduced glomerular filtration rate), essentially limiting the test validity (64) (Table 2).

An important modification of the urinary concentration test was proposed in the 1950s by Barlow and de Wardener (3). The authors aimed to improve the diagnostic value of urine concentration by adding the evaluation of the urine response to a subsequent injection of pitressin (3). They hypothesized that patients with CDI should respond with a further concentration of their urine, whereas patients with PP should not. In fact, except for two patients, all subjects in their study with PP (n = 8) revealed a greater urine concentration after dehydration than after pitrexin, despite significant variations in the absolute urine concentration during dehydration (Table 2). In contrast, all patients with CDI (n = 12) consistently showed a higher urine concentration after pitrexin than after dehydration. Similar findings were reported by Dies et al. (64), who found a decrease in urine osmolality after vasopressin injection in patients with PP (n = 2), but an increased urine concentration in CDI (n = 2) (Table 2). Thus, this test concept seemed much more promising than the evaluation of the absolute urine concentration alone. But, its validation in a larger series of patients showing the entire differential diagnostic spectrum of DI has long been missing.

A first standardized test protocol with detailed diagnostic test criteria was proposed by Miller et al. (67) in 1970 after the evaluation of 36 patients with different disorders of polyuria and polydipsia syndrome (Table 2). Patients with severe CDI (n = 18) were reported to fail in concentrating the urine above the level of plasma osmolality during dehydration but to feature a more than 50% urine osmolality increase (range, 51–792%) after exogenous vasopressin injection; patients with NDI (n = 2) showed a further rise of only 39 and 45%. In contrast, subjects with mild forms of CDI (n = 11) were able to concentrate their urine above their plasma osmolality but still demonstrated a further rise in urine concentration after vasopressin by more than 9% (range, 9–67%). A much higher urine concentrating ability was found in patients with PP (n = 3), who showed only a minor further increase in urine concentration after vasopressin, ranging between 2 and 13%.

Unfortunately, the diagnostic criteria derived from this study (67) (see Table 2 for details) have never been validated in an independent, prospective approach, and sensitivity and specificity for identification of differential diagnoses of DI have not been defined. Furthermore, it was shown that some patients with partial CDI may demonstrate quite normal urine concentrations, in particular in case of a decreased glomerular filtration rate (3, 64, 81). And the urine concentration ability may be variably reduced in different forms of chronic polyuria (82), leading to overlapping degrees of pathologically diminished urinary responses to osmotic stimulation (67). This diagnostic problem is not surprising, given some principles of kidney physiology. First, chronic polyuria itself can decrease the urinary concentration capacity (83–85), probably through a washout mechanism of the renal medullary concentration gradient as well as by down-regulation of kidney AQP2 water channels. Both may explain the same...
**TABLE 2.** Collection of the original data on the differential diagnosis of central diabetes insipidus in chronological order

<table>
<thead>
<tr>
<th>Year of study (Ref.)</th>
<th>Method of testing AVP reactivity</th>
<th>AVP: cc, c, p, v (volunteers)</th>
<th>Major findings in patients with CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1944 (79)</td>
<td>2.5% NaCl infusion</td>
<td>1. Tubular chloride reabsorbate (chloride R/P ratio); 2. urine flow (U-flow)</td>
<td>cc = 2, p = 1, v = 1. Cholate R/P is elevated at baseline and further increases during 2.5% saline infusion, but decreases in volunteers; 2. water diuresis persists during saline infusion</td>
</tr>
<tr>
<td>1947 (65)</td>
<td>2.5% NaCl infusion followed by pitressin injection</td>
<td>U-flow</td>
<td>Unchanged U-flow during saline infusion; prompt decrease after pitressin injection</td>
</tr>
<tr>
<td>1957 (96)</td>
<td>Serial infusion of nicotine, 2.5% NaCl, and pitressin under constant water-loading</td>
<td>FWC</td>
<td>Normal response to nicotine and pitressin, but no response to NaCl in 3 subjects with posterior pituitary damage; abnorlmal response to nicotine and normal response to NaCl in patients with PP</td>
</tr>
<tr>
<td>1959 (3)</td>
<td>Serial testing of vasopressin, 24-h dehydration alone, and followed by vasopressin</td>
<td>1. Maximum U-Osm during dehydration; 2. change in U-Osm after vasopressin</td>
<td>cc = 12, p = 8, v = 14. Maximum U-Osm reduced; 2. vasopressin-induced rise in U-Osm higher compared to PP</td>
</tr>
<tr>
<td>1961 (64)</td>
<td>Serial testing of dehydration, 0.5 mg nicotine, vasopressin, and 3% NaCl</td>
<td>1. Maximum U-Osm; 2. change in U-Osm due to vasopressin; 3. FWC</td>
<td>U-Osm during dehydration was lower and rise in U-Osm after vasopressin was higher compared to PP. Three subjects with CDI showed a partial response of FWC to nicotine, vasopressin, and saline; one subject with PP had a partial response to nicotine, but a good response to saline; the other one had completely normal responses</td>
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<td></td>
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<td>Urine-to-serum osmolality ratio is lower than in PP and volunteers</td>
</tr>
<tr>
<td>1963 (66)</td>
<td>Dehydration</td>
<td>Unr to-serum osmolality ratio</td>
<td>cc = 13, p = 3, v = 25</td>
</tr>
<tr>
<td>1967 (108)</td>
<td>5% NaCl infusion</td>
<td>1. U-flow; 2. U-Osm; 3. urine sodium excretion (U-Na+)</td>
<td>cc = 10, p = 3, v = 38. No change in U-flow, U-Osm, or U-Na+, contrary to patients with PP and volunteers</td>
</tr>
<tr>
<td>1970 (67)</td>
<td>Dehydration followed by vasopressin injection</td>
<td>1. Maximum U-Osm during dehydration; 2. change in U-Osm after vasopressin</td>
<td>cc = 18, c = 17, n = 2, p = 5, v = 10. In severe CDI and NDI, U-Osm remains below S-Osm during dehydration, and further rises by &gt;50% (CDI) or &lt;50% (NDI) after vasopressin. In partial CDI and PP, U-Osm rises to levels above S-Osm during dehydration, and further rises by &gt;9% (partial CDI) or &lt;9% (PP) after vasopressin</td>
</tr>
<tr>
<td>1980 (89)</td>
<td>5% NaCl infusion</td>
<td>Direct plasma AVP response to osmotic stimulation</td>
<td>cc = 3, c = 3, p = 4, v = 11. Plasma AVP response was found to be nondetectable (complete CDI, n = 3), subnormal (partial CDI, n = 3), or comparable (PP, n = 4) to healthy volunteers (n = 11)</td>
</tr>
<tr>
<td>1981 (86)</td>
<td>5% NaCl infusion</td>
<td>Direct plasma AVP response to osmotic stimulation</td>
<td>cc = 5, c = 5, p = 4</td>
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<tr>
<td>1981 (82)</td>
<td>5% NaCl infusion vs. dehydration test</td>
<td>Consistency in diagnoses of plasma AVP vs. urine concentration measurement (as described by Miller et al. as described in Ref. 67)</td>
<td>AVP: cc = 7, c = 8, n = 1, p = 7. WDT: cc = 7, c = 6, n = 0, p = 10. Both tests correctly identified complete CDI (n = 7). Two of six patients with partial CDI and three of 10 patients with PP, according to the dehydration test, had normal or subnormal AVP levels, respectively</td>
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<td>1983 (69)</td>
<td>5% NaCl infusion vs. dehydration test</td>
<td>Same endpoints as in Ref. 82</td>
<td>AVP: cc = 4, c = 9, n = 2, p = 6. WDT: cc = 7, c = 7, n = 0, p = 7. Both tests correctly identified PP (n = 6). Two of 4 subjects with undetectable AVP levels were confirmed as complete CDI by the dehydration test; one subject was diagnosed as partial CDI, one as NDI according to dehydration. And 8 of 9 patients with subnormal AVP levels were confirmed as partial CDI by the dehydration test, one patient was diagnosed as NDI</td>
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<td>1991 (97)</td>
<td>5% NaCl infusion followed by hydration-induced AVP suppression test</td>
<td>Diagnostic specificity of thirst rating on a visual analog scale for differing PP from CDI</td>
<td>cc = 7, p = 7, v = 7. Thirst sensation rises with elevating S-Osm, but is still consistently lower compared to PP. Oral hydration results in an immediate decrease in thirst, which is not seen in PP</td>
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<tr>
<td>1992 (99)</td>
<td>T1-weighted magnetic resonance imaging of the pituitary</td>
<td>Diagnostic specificity of the neurohypophyseal bright spot for differing PP from CDI</td>
<td>cc = 8, n = 4, p = 6, v = 92. Absent hyperintense signal of the posterior pituitary gland in all patients with CDI (n = 8), persistent signal in all patients with PP (n = 6), 3 of 4 patients with NDI, and in 90 of 92 patients without sellar disease</td>
</tr>
<tr>
<td>2011 (68)</td>
<td>Dehydration test</td>
<td>Direct comparison of: 1. the urine concentration tests (as described in Ref. 89); 2. direct plasma AVP measurement (as described in Ref. 89); and 3. direct plasma copeptin measurement against an independent diagnostic reference standard</td>
<td>cc = 17, c = 9, n = 2, p = 22, v = 30. Urine concentration tests with maximum U-Osm and change in U-Osm to vasopressin reached a diagnostic accuracy of 70%; plasma AVP correctly identified 38% of patients, and plasma copeptin identified 72% of patients</td>
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</table>

FWC, Free water clearance; S-Osm, serum osmolality; U-flow, urine flow; U-Na+, urine sodium excretion; chloride R/P ratio, relation of chloride concentration in the reabsorbate to that in plasma; U-Osm, urine osmolality; WDT, water deprivation test.
times lower than expected urinary response to injected vasopressin in CDI (86). Second, an enhanced antidiuretic response to low levels of plasma AVP has been reported (81, 87), possibly due to an up-regulated V2R expression in chronic states of CDI (88). On the other hand, patients with acquired NDI are often only incompletely resistant to AVP, and therefore may resemble patients with partial CDI. Thus, the consequence of these mechanisms is a convergence of different underlying disorders to a similar urinary phenotype. Accordingly, when we recently evaluated in a prospective study the diagnostic accuracy of the previously described urine concentration test (67) in 50 patients presenting the entire differential diagnostic spectrum of DI, we only found a total diagnostic accuracy of 41% (68) (Table 2).

Direct measurement of plasma AVP activity

With the availability of a first sensitive and specific AVP RIA in the 1970s, it was hoped that direct plasma AVP measurement would overcome the limitations of the urine concentration tests and allow a less cumbersome differential diagnosis of DI (87). The new test method, first implemented by Baylis and Robertson in the early 1980s (89, 90), exploited the direct assessment of AVP release in response to a 2-h hypertonic saline infusion test, and the data were interpreted as a function of the corresponding serum osmolality (Table 2 and Fig. 1). The conceptual superiority of this method was assumed to consist of an intact AVP responsivity to osmotic stimulation even after a long period of overhydration or dehydration (54). If compared with the normal physiological relationship between plasma AVP and serum osmolality (Fig. 1, gray area), patients with CDI were hypothesized to demonstrate data pairs below this area of normality, whereas patients with NDI or PP show data pairs above or within this normative area (89, 90) (Fig. 1 and Table 2).

Two peer-reviewed studies investigating the diagnostic performance of direct AVP measurements in differential diagnosis of DI are available in the literature. The first study, from Zerbe and Robertson (82) (Table 2), compared the diagnostic performance of plasma AVP measurement with that of the urine concentration test (67) in 23 patients. Patients with complete CDI (n = 7) could be easily identified by both test methods. Discrepant results, however, were found in patients with partial CDI and PP: two of six subjects diagnosed as partial CDI based on their urine levels revealed an entirely normal AVP response; one was later diagnosed as PP, the other as NDI. Vice versa, three of 10 patients diagnosed as PP by urine concentration had suppressed plasma AVP levels, clearly suggestive of AVP deficiency (82).

Similar diagnostic discrepancies between both test methods were reported by Milles et al. (69), who repeated the study in another 19 patients (Table 2). Both tests came to the diagnosis of PP in the same six patients, and also eight of nine patients with subnormal AVP levels could be confirmed as partial CDI by the urine test results; only one patient was diagnosed as NDI. But, two of four patients with undetectable plasma AVP levels were categorized as partial CDI (n = 1) or NDI (n = 1) according to their urine results.

An important difficulty in the interpretation of both studies is the lack of a diagnostic “gold standard” with which the test results could be compared. Thus, the final diagnosis and, therefore, the diagnostic accuracy of both test methods remain undetermined. Another critical point refers to the area of normality describing the physiological behavior of plasma AVP release in relation to the corresponding serum osmolality. The exact definition of this area is the fundamental basis for the identification of aberrant AVP secretion in patients tested for disease. On this crucial point, however, both studies (89, 90) relied on a previously described slope model of linear regression calculated on the basis of a very small number of healthy volunteers and without the definition of the corresponding reference area or stability limit (69, 87, 89). But more recent evidence, from a higher number of healthy controls, suggests that the relation between AVP and serum osmolality is less linear and close than has previously been described (68). Consequently, a total diagnostic accuracy of only 46% could be found when direct AVP measurement was prospectively tested in 50 patients with polyuria polydipsia disease (68) (Table 2). Finally, the well-characterized technical difficulties of the AVP assay with its high preanalytical instability (87, 91, 92) certainly also account for the still extremely low acceptance of the AVP assay in the differential diagnosis of DI.
Direct measurement of plasma copeptin (C-terminal proAVP)

A possibly novel approach to the diagnosis of DI offers the measurement of plasma copeptin in response to an appropriate osmotic stimulus. Within the last few years, copeptin, the C-terminal glycoprotein of the AVP prohormone, has been established as an easy to measure and stable surrogate for endogenous plasma AVP (91, 93, 94). Recent data have also promoted copeptin as a promising diagnostic marker for identification of patients with severe neurohypophyseal damage after transsphenoidal surgery (n = 38) (95).

Based on these findings, another prospective study evaluated the diagnostic potential of copeptin across the full differential diagnostic spectrum of DI (n = 50) (68) (Table 2). In accordance with the direct AVP test method (see The Urinary Concentration Test as an Indirect Measure of AVP Activity and Fig. 1), osmotically stimulated copeptin release was interpreted by plotting the hormone levels together with the corresponding serum osmolality into a nomogram and estimating the data pairs as to their position to the area of normality. In this way, copeptin revealed an overall diagnostic accuracy of 83%, whereas patients with complete CDI (n = 7) and NDI (n = 2) could already be identified at plasma baseline values. With respect to the particularly challenging differentiation of patients with PP and partial CDI, the ratio of copeptin increase during an 8-h dehydration period to the serum sodium concentration measured after 16 h of water deprivation (ΔCopeptin[8–16 h]/S-Na + [16 h]) proved to be a highly useful parameter, providing a diagnostic yield of 94%, and a specificity and sensitivity of 100 and 86%, respectively, to separate PP (n = 22) from partial CDI (n = 17) (Fig. 2). The main criticism to this approach, again, is the missing “gold standard” test with which the copeptin results could have been compared. To cope with this problem, the reference diagnosis in this study was made retrospectively, with consideration of patient history, clinical presentation, and treatment response. Moreover, the clinical use of copeptin levels as a surrogate of AVP secretion during osmotic stimulation still requires a larger database of normal and abnormal responses, and the reported diagnostic cutoff values that were determined in a post hoc analysis still need to be validated prospectively. Also important to note is the fact that the sandwich immunoluminometric copeptin assay (LUMItest CT-proAVP) is not yet commercially available in countries outside Europe, currently limiting its clinical implementation as a new diagnostic standard.

Further proposed test procedures

As might be expected, most patients with DI also exhibit a subnormal antidiuretic response to nonosmotic stimuli such as nicotine (96), hypotension, nausea, and hypoglycemia (90). But for diagnostic purposes, these nonosmotic tests of neurohypophyseal function do not provide advantages over the osmotic stimuli because they are difficult to control or quantitate and generally cause a markedly variable AVP response (90, 96). Moreover, they can lead to false-positive or false-negative test results because there are patients who exhibit little or no...
rise in AVP after hypotension or emesis, yet lack polyuria and have a normal response to osmotic stimuli. Conversely, patients with osmoreceptor dysfunction exhibit little or no antidiuretic response to hypertonicity but show a normal response to induced hypotension (35) or nicotine infusion (96) (Table 2).

An interesting diagnostic test method has been pursued by Thompson et al. (97) (Table 2), who examined the

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**FIG. 4.** Diagnostic approach to a patient with suspected diabetes insipidus. *, Findings suggestive for PP include: 1) history of psychiatric disease or neurotic personality, fluctuating symptoms and gradual onset of polydipsia; 2) posterior pituitary bright spot and normal thickness of the pituitary stalk; and 3) persistent polydipsia, development of hyponatremia after a therapeutic trial with desmopressin. ***, Findings suggestive for partial CDI include: 1) previous head trauma or pituitary surgery, family history of DI, recent and distinct onset of symptoms, consistent need of fluid intake during the night; preference for cold fluids; 2) missing pituitary bright spot and/or enlargement of the pituitary stalk beyond 2–3 mm; and 3) abolishment of thirst, polydipsia, and polyuria without development of hyponatremia after a standard dose of desmopressin. ***, Findings suggestive for partial nephrogenic diabetes insipidus include: 1) history of lithium or other drug therapies (e.g. cisplatin) interfering with urine concentration, presence of electrolyte disorders (like hypercalcemia or hypokalemia); 2) posterior pituitary bright spot and normal pituitary stalk; and 3) no effect of desmopressin on polyuria or polydipsia.
regulation of thirst sensation in patients with PP compared with DI. They found that patients with PP have a lower osmotic threshold for thirst than patients with DI and also show a resistance to nonosmotic inhibition of thirst. But similar to the urine-to-serum osmolality ratio, proposed by Dashe et al. (66) for differentiation between CDI (n = 13) and PP (n = 3) (Table 2), both test methods did not gain wide acceptance in clinical routine and also lack validation.

In recent years, cMRI has emerged as another useful addition to the biochemical tests in the diagnosis of DI. The physiological bright spot in the posterior pituitary of the sella turcica, best seen in sagittal views on T1-weighted images (98), is persistent in patients with PP (n = 6) (99) (Table 2 and Fig. 3A) and is absent in CDI (n = 8) (Fig. 3B). But also here, individual cases of CDI with persistent pituitary bright spot have been reported (100, 101) most likely due to an early stage of the disease, whereas an age-related absence of the signal has been described in up to 20% of normal subjects (102). Conversely in NDI, the bright spot is present in some patients and absent in others (103). Consequently, the role of cMRI as a diagnostic test in patients with DI remains to be clarified. It has been suggested that cMRI is a more useful tool for ruling out than for ruling in a diagnosis of CDI (104). A very similar conclusion also seems to apply to measurements of the pituitary stalk, whose enlargement beyond 2–3 mm has been considered to be pathological (105), but not necessarily to be specific for idiopathic CDI (106). The situation is quite different when the cMRI scan shows both thickening of the stalk and an absent neurohypophyseal bright spot; in this case, idiopathic CDI and systemic diseases should seriously be considered (104).

A therapeutic trial with a standard dose of desmopressin for several days may be another useful approach in case of persistent diagnostic uncertainty (107) (Fig. 4). Although such a therapeutic trial is a plausible diagnostic concept, sufficient evidence for its diagnostic accuracy is still missing, and it may carry significant risks. Thus, it should be conducted under close supervision.

Diagnostic Implementations and Future Perspectives

Our analysis reveals a surprisingly poor database without sufficient validation of the current diagnostic test standards for differentiation of DI. The data reported also make clear that no agreement exists today regarding how to biochemically best diagnose DI, and also that the commonly followed test protocols suffer from poor diagnostic accuracy. These limitations are important to know and should encourage the clinician to interpret the diagnostic test results with great caution. For the time being, we consider the water deprivation test followed by a desmopressin challenge as the most plausible test standard to validate the adequacy of AVP function (Fig. 4). In patients with a seriously impaired urine concentration capacity (urine osmolality <300 mOsm/kg), increases in urine osmolality in response to desmopressin administration of more than 50% reliably indicate complete CDI, and responses of less than 50% indicate complete NDI. Responses between less than 0 and less than 50% in patients with only mild or moderately impaired urine concentration capacity (urine osmolality >300 to <800 mOsm/kg) are diagnostically indeterminate. In these cases, measurement of plasma AVP may be useful, provided that it is performed with a sensitive and validated assay for AVP, reliable preanalytical handling of samples is guaranteed, and corresponding serum osmolality is in the hypertonic range, preferably above 300 mOsm/kg. Otherwise, the differentiation between PP, partial CDI, and partial NDI should currently rely on a comprehensive assessment of patient and family history, clinical data, cMRI imaging of the hypothalamic-pituitary region, and a therapeutic trial with desmopressin (Fig. 4).

There are emerging data on copeptin measurement in the differential diagnosis of DI to suggest that this surrogate provides a novel and more robust test concept of neurohypophyseal function than current test standards. But importantly, before its implementation in differential diagnostic routine procedures, previous findings on copeptin in DI still need to be confirmed in larger prospective trials. The ultimate aim should be to use the diagnostic potential of copeptin for a simplification of the currently still cumbersome diagnostic workup of DI.

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