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Diagnosis and management of diabetes insipidus for the internist: an update

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Diabetes insipidus is a disorder characterized by excretion of large amounts of hypotonic urine. Four entities have to be differentiated: central diabetes insipidus resulting from a deficiency of the hormone arginine vasopressin (AVP) in the pituitary gland or the hypothalamus, nephrogenic diabetes insipidus resulting from resistance to AVP in the kidneys, gestational diabetes insipidus resulting from an increase in placental vasopressinase and finally primary polydipsia, which involves excessive intake of large amounts of water despite normal AVP secretion and action. Distinguishing between the different types of diabetes insipidus can be challenging. A detailed medical history, physical examination and imaging studies are needed to detect the aetiology of diabetes insipidus. Differentiation between the various forms of hypotonic polyuria is then done by the classical water deprivation test or the more recently developed hypertonic saline or arginine stimulation together with copeptin (or AVP) measurement. In patients with idiopathic central DI, a close follow-up is needed since central DI can be the first sign of an underlying pathology. Treatment of diabetes insipidus or primary polydipsia depends on the underlying aetiology and differs in central diabetes insipidus, nephrogenic diabetes insipidus and primary polydipsia. This review will discuss issues and newest developments in diagnosis, differential diagnosis and treatment, with a focus on central diabetes insipidus.

Keywords: copeptin, diabetes insipidus, primary polydipsia, water deprivation test, diagnosis.

Introduction

Diabetes insipidus (DI) is a rare disease with a prevalence of ~ 1 in 25 000 individuals. The disorder can manifest at any age, and the prevalence is similar amongst males and females.

Diabetes insipidus is a form of polyuria–polydipsia syndrome and is characterized by excessive hypotonic polyuria (>50 mL/kg body weight/24 h) and polydipsia (>3 L/day) [1]. After exclusion of disorders of osmotic diuresis (such as uncontrolled diabetes mellitus), the differential diagnosis of DI involves distinguishing between primary forms (central or renal) and secondary forms (resulting from primary polydipsia). A third, rare form of DI termed gestational DI can occur during pregnancy and is not further discussed here. Central DI results from inadequate secretion and usually deficient synthesis of arginine vasopressin (AVP) in the hypothalamic–neurohypophyseal system in response to osmotic stimulation (Figure 1) and can be acquired or (less often) hereditary [2]. Nephrogenic DI is the result of resistance of the kidneys to AVP, either due to mutations in the gene encoding arginine vasopressin receptor 2 (*AVPR2*) or aquaporin 2 (*AQP2*) [3] or as an adverse effect of drugs or due to electrolyte disorders. Primary polydipsia is characterized by excessive fluid intake that consecutively leads to polyuria, despite intact AVP secretion and an appropriate antidiuretic renal response.

Regardless of the aetiology, all forms of the polyuria–polydipsia syndrome result in a water diuresis due to an inability to concentrate urine maximally.

Differentiating between these types is important, as treatment strategies differ and application of the wrong treatment can be dangerous [4]. However, an accurate diagnosis is often difficult [5], especially in patients with primary polydipsia or partial forms of central and nephrogenic DI [1]; see above.

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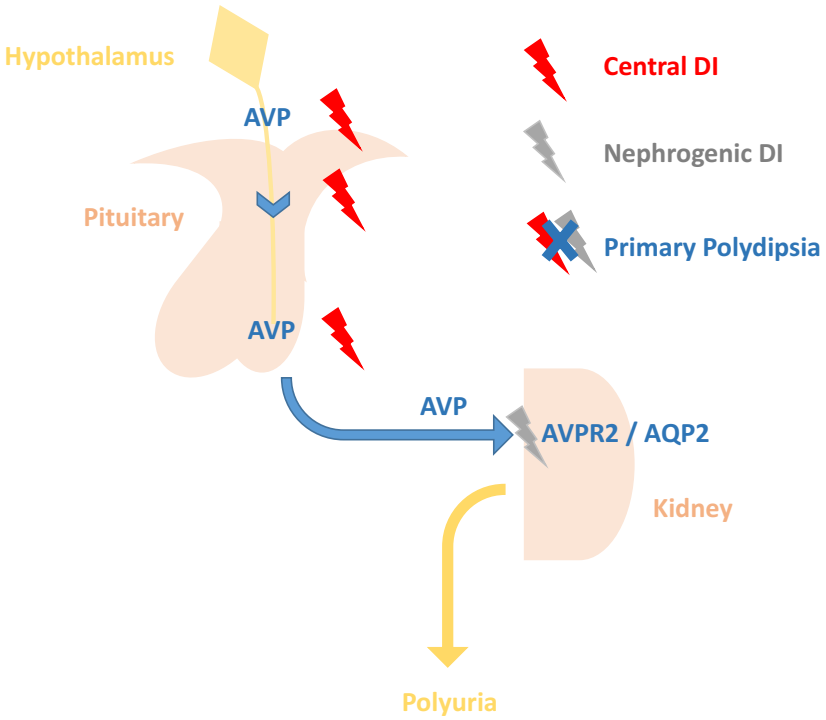

Fig. 1 *AVP action in central and nephrogenic diabetes insipidus a primary polydipsia.*

In this review, we will describe the different types and aetiologies of DI, the typical clinical manifestation, and also focus on clinical consequences of central DI besides polyuria. In addition, we will detail which initial laboratory and radiological investigations should be performed, and which specialist investigations (stimulation tests) currently are recommended. Lastly, we will discuss treatment options, especially in central DI, not only by the specialist in the ambulatory setting but also by general internal medicine experts in the emergency situation.

Aetiologies of polyuria–polydipsia syndrome

Diabetes insipidus – both central and nephrogenic – may be hereditary or acquired. Acquired forms of DI are much more common than hereditary forms, which account only for approximately 6–10% of DI cases [6]. Table 1 gives an overview of acquired and hereditary forms of DI. Acquired forms of central DI develop secondary to neurohypophysis or hypothalamic median eminence lesions leading to deficient synthesis or secretion of AVP. Damage by local compression may arise from primary brain tumours (e.g. craniopharyngioma, germinoma) or metastasis. Central DI due to pituitary adenomas is rare, but postoperative DI after resection of adenomas or other pituitary tumours is the most common cause of acquired central DI and is observed in ~ 20% of pituitary surgery [7]. Postoperative DI is often transient, but depending on the extent of neuronal destruction, permanent disease may develop.

More rare causes of acquired central DI are hypophysitis, infiltrative disorders (such as histiocytosis, sarcoidosis) or infectious diseases (meningitis, encephalitis, tuberculosis). Finally, in up to 25–50% of patients with adulthood-onset central DI, no underlying disease can initially be identified and these cases are referred to as idiopathic DI.

Hereditary forms should be suspected if DI manifests early in life and when a positive family history is present. In fact, the predominant inheritance pattern in central familial DI is autosomal dominant and develops on the basis of a mutation in the *AVP* gene [8]. More seldom, central DI is caused by an autosomal recessive disorder

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Table 1. *Aetiologies of polyuria–polydipsia syndrome*

Central diabetes insipidus		
Acquired	Postoperative or trauma	Pituitary surgery
		Deceleration injury
		Radiotherapy
	Primary brain tumours	Craniopharyngioma
		Meningioma
		Germinoma
		Rathke's cleft cyst
		Pituitary adenoma
		Astrocytoma
	Metastatic cancer	Lymphoma
		Breast cancer
		Lung cancer
	Infiltrative	Neurosarcoidosis
		Langerhans cell histiocytosis
	Inflammatory/autoimmune	Lymphocytic hypophysitis Granulomatous hypophysitis
		Xanthomatous hypophysitis
		IgG4-related hypophysitis
	Infectious	Meningitis
		Encephalitis
		Tuberculosis
	Idiopathic	
Hereditary	Mainly affected gene	*AVP*
Nephrogenic diabetes insipidus		
Acquired	Drugs	Lithium
		Cisplatin
		Demeclocycline
	Electrolyte disorders	Hypokalaemia
		Hypercalcaemia
	Haematological	Multiple myeloma
		Amyloidosis
		Sickle cell disease
Hereditary	Mainly affected genes	*AVPR2, AQP2*
Gestational diabetes insipidus		
	Increased AVP degradation	By placental vasopressinase
Primary polydipsia		
	Psychogenic	Hypothalamic lesions
	Habitual	
	Somatic	
	Beer potomania	

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(Wolfram's syndrome) due to a mutation in the gene *WFS1* [9].

In nephrogenic DI, the concentrating ability of the nephrons is impaired due to renal resistance to AVP. Lithium therapy is the most frequent cause of acquired nephrogenic DI and may be reversible if lithium is removed. However, long-term treatment with lithium (>18 years of exposure) likely results in permanent nephrogenic DI [10]. Besides drugs, electrolyte disorders such as hypokalaemia or hypercalcaemia may promote (reversible) nephrogenic DI probably via a temporary downregulation of aquaporin 2 (AQP2) expression [11].

The majority (>90%) of hereditary nephrogenic DI cases are due to X-linked loss-of-function mutations in the *AVPR2* gene resulting in a dysregulation of the AVPR2 [12,13]. More than 250 *AVPR2* mutations have been identified and lead to complete AVP deficiency in male patients. Heterozygous female patients are sometimes also affected by various degrees in case of skewed X chromosome inactivation [12]. The remaining 10% of hereditary nephrogenic DI are explained by loss-of-function mutations in the *AQP2* gene (>60 disease-causing mutations have been identified), which may be inherited in either autosomal recessive or autosomal dominant fashion [3].

Both central DI and nephrogenic partial DI may be unmasked during pregnancy when AVP is increasingly degraded by the placental enzyme vasopressinase (gestational DI) [14].

Primary polydipsia is most often associated with psychiatric diseases such as schizophrenia, schizoaffective or bipolar disorders [15], but has also been described in patients with anxiety and anorexia or other dependency disorders [16]. Interestingly, primary polydipsia seems increasingly prevalent in health-conscious individuals who wish to increase their well-being by excessive water intake [16,17]. Whether or not an underlying psychopathology is present, primary polydipsia can be categorized as psychogenic or habitual polydipsia. A comparable disorder is beer potomania, which is characterized by consumption of large amounts of beer, usually accompanied by low solute intake increasing the risk of hyponatraemia and fluid intoxication. The pathophysiological basis of primary polydipsia has not been completely understood. Neural and functional changes in the thirst centre and the hippocampal region have been suggested to contribute to the altered regulation of fluid intake in primary polydipsia [18,19]. Besides psychopathological or habitual factors, primary polydipsia can also be caused by hypothalamic lesions damaging thirst regulation [4]. These lesions may be the same as those found in central DI; see Table 1.

Diagnosis of diabetes insipidus

Clinical manifestation

Given the different aetiology of polyuria–polydipsia syndrome doctors, one factor to correctly diagnose polydipsic patients is according to the rapidity of symptom onset and the severity of symptoms. Sudden onset, persistent symptoms during the night and preference for cold beverages were considered typical of diabetes insipidus, whilst a high incidence of psychiatric disorders was believed to be in patients with primary polydipsia. However, a recent evaluation of 156 polyuria–polydipsia patients [20] found a similar amount of fluid intake and excretion in patients with central DI and PP (median litres consumed/excreted per day (IQR): central DI 6 (5–8)/5 (4–8); PP 5 (5–7)/5 (4–6)). Furthermore, the majority in both groups indicated a preference for cold drinks (central DI: 75%; PP: 60%) and persistent symptoms during the night (drinking at night/nycturia: central DI: 92%/95%; PP: 62%/68%). Psychiatric comorbidities were not exclusively seen in PP but also seen in DI (27% in PP and 17% in central DI). The only noticeable difference was the rate of onset of symptoms, which appeared suddenly in 63% of the central DI patients compared with only 22% of the PP patients. However, it is important to keep in mind that central DI due to AVP mutations, inflammatory syndromes or postradiation will also typically show a slow onset.

Accordingly, whilst clinical symptoms are helpful in indicating the possible aetiology of the polyuria–polydipsia syndrome, they are not specific enough to distinguish DI from PP.

Clinical consequences of AVP deficiency besides polyuria

Interestingly, lack of AVPR2 activation with consecutive polyuria has been the only major clinical issue associated with AVP deficiency (central DI) so far. However, AVP is involved in a wide range of physiological regulatory processes beyond water reabsorption. AVPR1a and AVPR1b are found not only in the periphery, but also in different areas

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throughout the brain [21,22], that is AVP1b receptors are heavily expressed on the anterior pituitary corticotropes. As AVP is a well-known regulator of the hypothalamus–pituitary–adrenal (HPA) axis, one would expect altered stress physiology in DI. In fact, several reports have indicated different (typically enhanced) HPA response patterns after various stimuli (i.e. CRH administration, hypertonic saline, arginine infusion) in DI patients versus healthy controls [23–25]. One explanation includes the upregulation of CRH receptors in DI leading to an increased sensitivity of pituitary ACTH-producing cells to CRH stimulus. Although this distinct HPA response pattern in DI is quite consistently described in the literature, the clinical impact of this finding remains completely unknown.

An increasing amount of data – mostly in rodents – implicates that AVP via central AVPR1a and AVPR1b activation may also be involved in aspects of social behaviour such as aggression, social memory and emotionality [26,27]. In humans, polymorphisms in the *AVP1a* gene have been linked to autism spectrum disorder and cognitive dysfunction, supporting this hypothesis [28,29]. Recently, studies have shown a greater prevalence of psychopathologies in patients with hypopituitarism and again a role of AVP or oxytocin has been speculated [30,31]. However, only very limited data are available specifically describing patients with hypopituitarism and central DI [32]. Clearly, the role of AVP and oxytocin in social behaviour and cognitive brain function and its potential implications for DI patients needs further investigation.

In the periphery, AVPR1a is primarily involved in vasoconstrictive responses in vascular tissue. The regulation of systemic blood pressure, vascular tonus and blood volume is very complex, and the precise contribution of AVPR1a has not fully been defined [21]. Lack of AVPR1a activation in DI patients does not seem to have a major impact on blood pressure regulation.

AVP deficiency in central DI is associated with chronic low uric acid clearance and hyperuricaemia. Volaemia is an important determinant of uric acid regulation, but AVP by its action on AVPR1 has also been speculated to play a role in uric acid clearance [33,34,35]. The clinical consequence of the potentially altered uric acid metabolism in DI patients remains unclear. In our experience, DI patients do not suffer more often from urate crystal formation and deposition. In the literature, we found single case reports of gouty arthritis associated with DI. However, those patients may have had other risk factors for the clinical expression of hyperuricaemia.

Finally, a recent study suggested a direct role of AVP on haematopoiesis as expression of all three AVPRs was found on haematopoietic stem cells in rodents and in humans [36]. However, to date, there is limited evidence that this may have important clinical consequences in DI patients [37].

Initial investigations

A careful stepwise approach is recommended when evaluating patients presenting with the polyuria–polydipsia syndrome (*see* Figure 2).

The assessment of the medical history should include timing and onset of symptoms, their severity and possible triggering factors. In addition, a history of head trauma, headaches, vision disturbances and signs for anterior pituitary dysfunction should be enquired. The medical history should include questions about psychiatric and dependency disorders and a thorough drug history. Obtaining the family history is important for possible hereditary causes [2].

To assess potential dehydration, evaluation of the volume status besides routine measurement of blood pressure and heart rate should be performed. Because suprasellar extension of pituitary adenoma can cause visual impairment due to compression of the optic chiasm [38], a visual test including assessment of diplopia and visual field defects is recommended. Rare causes of polyuria–polydipsia syndrome are inflammatory or vascular disorders, which might be detected through a comprehensive skin and lymph nodes assessment.

Once secondary causes such as diabetes mellitus, hypercalcaemia or hypokalaemia are excluded, the presence of hypotonic polyuria (<800 mOsm/kg; >50 mL per kg body weight per 24 h) should be confirmed by 24-h urine collection [1]. The measurement of plasma sodium and osmolality levels then helps to indicate the cause of the polyuria–polydipsia syndrome. The presence of hyponatraemia (plasma sodium < 135 mmol/L) or low plasma osmolality (<280 mOsm/kg) is highly

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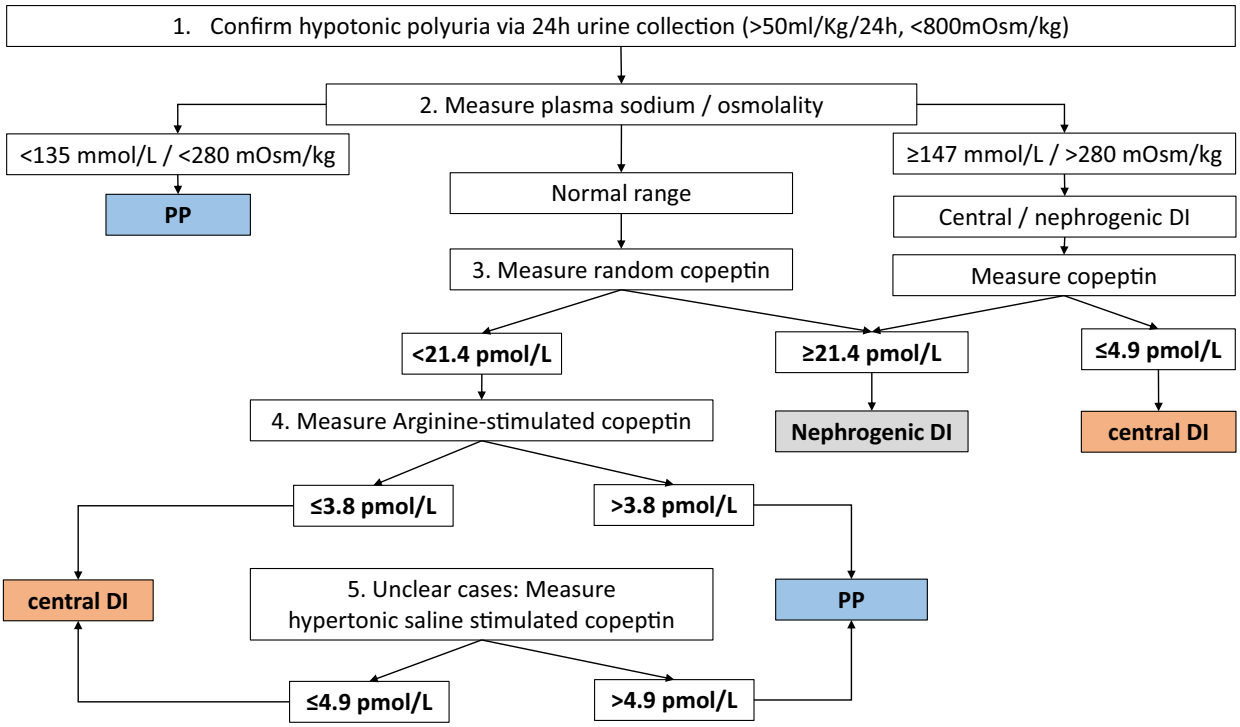

Fig. 2 *Diagnostic approach to polyuria–polydipsia syndrome.*

suspicious for PP [39]), whilst a high plasma sodium (≥147 mmol/L) and/or plasma osmolality (>300 mOsm/kg) points towards DI [40]. However, most polyuria–polydipsia patients will present with sodium and osmolality levels within the normal range [20], making additional tests necessary.

Radiological investigations

In patients with confirmed polyuria–polydipsia syndrome, performing a pituitary magnetic resonance imaging (MRI) can help narrow down the differential diagnoses. In addition to adenoma, infiltrative or inflammatory changes in the posterior pituitary, there are two findings, which have been described to be pathognomonic for central DI. One is the absence of the so-called bright spot, an area of hyperintensity in the posterior pituitary gland possibly resulting from stored AVP in neurosecretory granules [41,42]. Whilst a prospective evaluation of pituitary MRIs of 92 patients with polyuria–polydipsia syndrome indeed confirmed the absence of the bright spot in 70% of patients with central DI [20], this characteristic area was also missing in 39% of patients later diagnosed with PP. This could be due to an age-related reduction in the bright spot, as has been reported for the majority of healthy subjects in another study [43]. Interestingly, there are also several case reports of persistent bright spots in central DI patients [6,44]. These patients may have been in the early stages of their disease. Alternatively, the bright spot could reveal oxytocin – the other hormone of the posterior pituitary – instead of AVP storage. The second characteristic finding for central DI is a thickened pituitary stalk, defined as a pituitary stalk diameter above 3.5 mm [45]. Whilst pituitary stalk thickening can point towards inflammatory or infiltrative diseases, it can also be idiopathic and is not specific for central DI [20,46]. Thus, whilst an enlarged pituitary stalk or absence of bright spot on pituitary MRI should trigger further investigations focusing on possible underlying disorders, these findings should not be used as a sole diagnostic criteria for diagnosing central DI.

Specialist investigations

Since in most of the cases neither the medical history, clinical examination, laboratory evaluation nor pituitary MRI leads to a clear diagnosis, further tests are required. The following sections will discuss the current testing protocols available. A

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Diagnostic test	Test procedure	Test duration	Test evaluation	Diagnostic accuracy	Limitations
Basal copeptin measurement	Measurement unstimulated copeptin level	10 minutes	Copeptin > 21.4 pmol/L diagnoses nephrogenic DI	100% Sensitivity 100%, specificity 100% (54)	• Only small number of partial nephrogenic DI patients were included in studies (53,54)
Water deprivation test	• Water deprivation for 17 hours. • Administration desmopressin after 16 hours	≥17 hours	• cDI: urine osmolality <300 mOsm/kg, increase upon desmopressin >50% • nDI: urine osmolality <300 mOsm/kg, increase upon desmopressin <50% • pDI: urine osmolality 300-800 mOsm/kg, increase upon desmopressin >9% • PP: urine osmolality 300-800 mOsm/kg, increase upon desmopressin <9%	70-77% Sensitivity 86%, specificity 70% (20)	• Low diagnostic accuracy • Long test duration • Usually overnight stay patients required • Risk of post-test hyponatremia through excessive water intake / high sensitivity to desmopressine injection (20)
Hypertonic saline infusion test	3% hypertonic saline infusion: • Bolus 250ml within 15 minutes • Body weight adapted rate: 0.15 ml per kg body wieght per minute • Rapid sodium measurements every 30 minutes, stopp infusion and measure copeptin once sodium >147 mmol/L • Relower sodium with infusion glucose 5% 500ml and fluid intake 30ml/kg body weight	2-3 hours	• cDI: Copeptin ≤4.9 pmol/L • PP: Copeptin >4.9 pmol/L	97% Sensitivity 93%, specificity 100% (20)	• Close monitoring and access to rapid sodium measurements pre-exquisite to perform test • Risk of osmotic overstimulation
Arginine stimulation test	Arginine infusion: • 0.5g L-Arginine Hydrochloride 21% per kg body weight (max 40g) diluted in 500ml NaCl 0.9% • Administrate infusion over 30 minutes • Measure copeptin 60 minutes after start of infusion	1-2 hours	• cDI: Copeptin ≤3.8 pmol/L • PP: Copeptin >3.8 pmol/L	93% Sensitivity 92%, specificity 93% (57)	• Test must be interpreted with care in case of vomitus • Prospective validation study currently ongoing

Fig. 3 *Characteristics of available diagnostic tests.*

proposed stepwise approach towards the diagnosis of diabetes insipidus is shown in Figure 2 and an overview over the possible test methods and their limitations in Figure 3.

Baseline copeptin measurement

Copeptin derives from the precursor protein pre–pro-vasopressin together with AVP and neurophysin II [47,48]. Several studies have shown that copeptin mirrors AVP concentration and has shown an even higher correlation to plasma osmolality than AVP [49,50]. Whilst AVP measurement failed to enter clinical practice because of complex preanalytical requirements and only few reliable assays available [51], copeptin has the advantage that it is stable for several days at room temperature, does not require preanalytical procedures and can be measured within two hours in 50ul serum or plasma. With the original manual sandwich immunoluminometric assay (LIA) [52] and its successor the automated immunofluorescent assay (KRYPTOR platform), there are currently two CE certified assays available.

The promising role of copeptin as a diagnostic marker for DI was first shown in two prospective studies [53,54]. They revealed that unstimulated copeptin levels, that is copeptin levels taken before water deprivation or stimulation tests, that exceed 21.4 pmol/L show a 100% sensitivity and specificity for the diagnosis of nephrogenic DI. Whilst these basal copeptin levels obviate the need for further testing for nephrogenic DI, they cannot be used to differentiate central DI from PP patients because of their large overlap. Accordingly, further stimulation tests are needed for those two groups.

The water deprivation test

The water deprivation test according to the test protocol proposed by Miller et al. [55] has been the standard test to diagnose DI for many years. It is also often referred to as the indirect water deprivation test, since it does not include direct AVP measurement but instead assesses the AVP effect indirectly by measuring the urine concentration over 17 h of period of fluid deprivation. One hour before the end of the test desmopressin, a synthetic AVP analog is administered and changes in urine osmolality are taken into account for the diagnostic evaluation. Urine osmolality below 300 mOsm/kg despite water deprivation diagnoses complete DI, with patients with central DI showing an increase

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in urine osmolality above 50% upon desmopressin injection, whilst patients with nephrogenic DI remain below this threshold. Patients with partial central DI or PP usually increase with their urine osmolality to 300–800 mOsm/kg. Upon desmopressin injection, partial central DI patients show an increase in urine concentration of more than 9%, whilst this increase is less than 9% in PP patients. However, it is important to note that these cut-offs were derived from post hoc assessment of a single study involving only 36 patients without prospective validation [55]. Furthermore, the diagnostic cut-offs show a large overlap, especially in the two patient groups partial central DI and PP. This is best explained by the reduction in the renal medullary concentration gradient in longstanding PP patients, which makes any diagnostic evaluation of the urine osmolality difficult [56]. Two prospective studies [20,53] revealed these issues by showing a low diagnostic accuracy of only around 70% of the water deprivation test with particularly poor performance for diagnosing PP. Additional copeptin measurement during the water deprivation test further reduced its diagnostic accuracy and is therefore not recommended [20].

The hypertonic saline stimulation test

With the discovery of copeptin as a stable AVP surrogate marker, the concept of direct testing was revisited. Since the osmotic stimulation of the water deprivation test is insufficient [20], the administration of a 3% hypertonic saline infusion was evaluated. In a first study involving 50 patients with polyuria–polydipsia syndrome [54], patients were first deprived from water for 5 hours and received additional infusion of 3% hypertonic saline if needed with the aim to increase plasma sodium levels above 147 mmol/L. At this threshold, a copeptin level above 4.9 pmol/L diagnosed patients with PP with a 94% sensitivity and specificity. This copeptin cut-off has recently been prospectively validated in the so far largest cohort of 156 polyuria–polydipsia syndrome patients [20]. Instead of the initial water deprivation period, the test protocol in this study was further simplified by administrating only 3% hypertonic saline solution (first as a 250ml bolus followed by a body weight-adapted infusion rate) aiming at a plasma sodium level ≥ 150 mmol/L. Using the previously defined copeptin cut-off level of 4.9 pmol/L confirmed the high diagnostic accuracy of 97% (sensitivity 93%, specificity 100%) of the hypertonic saline stimulation test to differentiate patients with PP from patients with central DI.

The short test duration of 2–3 hours, making it possible to perform this test in the outpatient setting, is a further advantage. In addition, the majority of patients undergoing both tests stated that they preferred the hypertonic saline infusion over the water deprivation test [20] despite a higher rate of adverse events such as vertigo or malaise. Nevertheless, this test should only be performed in centres where the rise in sodium levels can be closely monitored using rapid sodium measurements (e.g. venous blood gas analysis) to prevent osmotic overstimulation and to ensure the safety of the test.

The arginine stimulation test

Recent data revealed the amino acid arginine as another stimulator of the posterior pituitary [57]. Arginine is an endogenous precursor to nitric oxide, an important signalling molecule in several endocrine pathways, and is used in clinical practice as a standard test for stimulating growth hormone [58]. The current prospective study included 92 healthy adults and children and 96 patients with polyuria–polydipsia syndrome [57]. The arginine infusion led to a rise in the median copeptin levels from 5.2 pmol/L to 9.8 pmol/L in the healthy participants. Meanwhile, a copeptin level of 3.8 pmol/L taken 60 min after start of the infusion had a high diagnostic accuracy of 93% (sensitivity 92%, specificity 93%) to distinguish the 38 central DI from the 58 PP patients. Another advantage of the arginine infusion test is that it is well-tolerated, with adverse effects mainly involving mild nausea. If a patient experiences severe nausea or vomiting, test results should be interpreted with caution as vomiting is a potent trigger for AVP/copeptin release.

A post hoc evaluation compared the results of 60 patients who underwent the hypertonic saline infusion test [20] and the arginine infusion test protocol [57]. This comparison showed a higher diagnostic accuracy for the hypertonic saline infusion test of 100% compared with 93% of the arginine infusion test, which is probably due to the stronger copeptin stimulation by hyperosmolality. A clear advantage of the arginine infusion test, however, is its simple and short test procedure without constant rapid laboratory assessments and its good tolerability. To validate the

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derived arginine-stimulated copeptin cut-off levels and for a prospective comparison with the hypertonic saline infusion test, a randomized multicentre study is currently being carried out (clinical trials.gov NCT03572166). First results are expected in 2022.

In summary of the above-mentioned tests, it can be said that copeptin measurement has become an important biomarker for the diagnosis of DI. Whilst basal copeptin measurement easily diagnoses nephrogenic DI, two copeptin stimulation tests with a high diagnostic accuracy are available to differentiate central DI from PP patients.

How to proceed in case of idiopathic DI

Differential diagnosis of central DI is challenging when clinical evidence of a causal injury or a specific disease is not present (idiopathic DI). The pituitary MRI may show no abnormality or just the absence of the bright spot or unspecific pituitary stalk thickening. The aetiological spectrum of idiopathic DI includes autoimmune/inflammatory or infiltrative diseases, neoplasia or congenital anomalies in the presence of pituitary stalk lesions [59]. Biopsies of the pituitary stalk are rarely performed due to the critical localization and associated morbidity.

In the literature, a standardized evidence-based diagnostic approach to idiopathic DI is lacking. However, given the possibility of an occult pathological process, a broad initial evaluation and an appropriate endocrine follow-up are indicated. Our approach to patients with idiopathic DI is illustrated in Figure 4.

We recommend routine clinical and laboratory evaluation of concomitant anterior pituitary deficiency, which may be present in up to 50% either at diagnosis or during follow-up [6]. Additionally, we perform a broad laboratory assessment (including renal and liver function test, C-reactive protein, erythrocyte sedimentation rate and blood count). A lumbar puncture may be performed in case of severe headache or according to the clinical context.

The presence of other autoimmune disorders (e.g. hypothyroidism, type 1 diabetes, Addison's disease) may point to an possible autoimmune

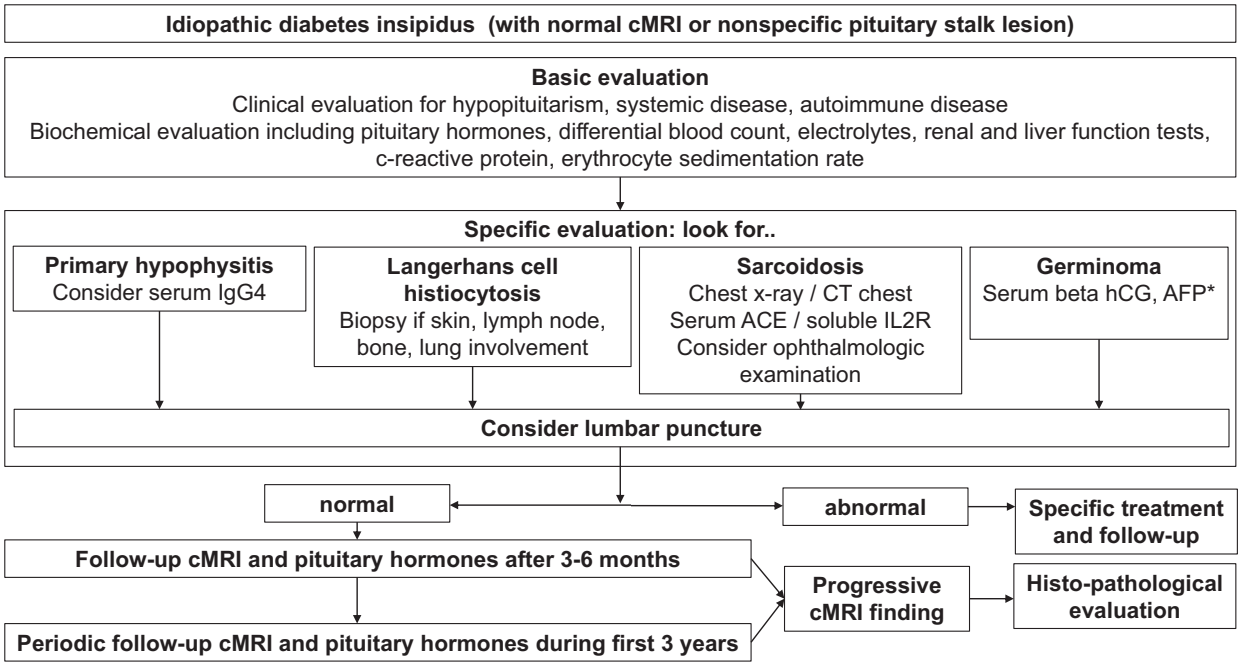

Fig. 4 *Diagnostic approach to idiopathic diabetes insipidus.*

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aetiology such as hypophysitis [44]. This rare pathology with different histopathological variants has a female preponderance and may be associated with pregnancy. According to a large German series of 76 patients with primary hypophysitis, central DI is present in over 50% of patients and mostly associated with other pituitary deficits such as hypogonadism, hypothyroidism or adrenal insufficiency [60]. Common nonendocrine symptoms are headache and increasing body weight as a sign of hypothalamic involvement [60]. Autoantigens involved in autoimmune DI and the role of antibodies directed against AVP-secreting cells have not been fully elucidated [61], and we do not routinely measure antibodies in idiopathic DI. According to an Italian study involving 150 patients, antibodies are present in one third of patients with idiopathic DI and in one quarter of patients of other forms of central DI [62]. Various brain tumours, especially germinoma, are also associated with the development of hypothalamic–pituitary antibodies [63]. Pituitary antibodies are, therefore, not specific nor sensitive and may rather represent an epiphenomenon. A rare form of hypophysitis represents IgG4-related hypophysitis, which may be associated with other IgG4-related systemic diseases (e.g. retroperitoneal fibrosis, autoimmune pancreatitis, lung or lymph node involvement). IgG4-related hypophysitis seems more prevalent in men above 55 years and is probable if elevated serum IgG4 levels, tissue infiltration of IgG4-positive plasma cells and/or typical organ involvement is present [64].

Langerhans cell histiocytosis is a rare disease, which is characterized by histiocyte tissue infiltration. The prevalence is highest in young children, but the disease is seen in all age groups. Nearly every organ may be affected, but bone, skin, lung or lymph node involvement is most commonly observed [65]. The disease may be limited to one organ (in more than half of patients) or manifests as a multisystem illness. Central DI is the most frequent endocrine manifestation and may represent the first symptom of Langerhans cell histiocytosis [66]. Patients with idiopathic DI should, therefore, be carefully assessed for concomitant or later onset of other organ manifestation of Langerhans cell histiocytosis, which typically arises within the first two years of DI diagnosis [6,67]. The diagnosis is confirmed by pathologic evaluation of involved tissue.

Sarcoidosis is another multisystem infiltrative disorder that may manifest with hypothalamic or pituitary involvement. The screen for sarcoidosis should include a careful evaluation of skin and lymph nodes and an ophthalmologic examination or lumbar puncture may be useful. We measure angiotensin-converting enzyme (ACE) and/or soluble interleukin-2 receptor (IL2R) in serum and perform a chest X-ray (a quarter to two third of patients with neurosarcoidosis have suggestive lung findings) although none of these tests have perfect sensitivity or specificity [68,69].

Germinomas have a peak incidence in the second decade of life and manifest more often in males compared with females, and the most frequent intracranial sites include the suprasellar region and the pineal gland. Germinomas can be screened by measuring the tumour markers alpha-fetoprotein and beta-hCG in serum (and cerebrospinal fluid); however, these tumour markers are not specific. High markers are typically seen in other germ cell tumours such as choriocarcinomas and immature teratomas, but low or normal markers are observed in pure germinomas or mature teratomas. If central DI is the first disease manifestation of a germinoma, the correct diagnosis is often delayed [70]. Serial imaging during the first three years is important as radiological signs (e.g. progressive thickening of the pituitary stalk) may only be apparent over time [6,46].

To exclude fast-growing malignant tumours that need prompt histopathological evaluation, we perform the first imaging three to six months after the initial diagnosis of central DI. Thereafter, the frequency of repeated imaging is individualized according to the clinical context and whether or not abnormal MRI findings are present. If the MRI shows normal findings, a yearly MRI seems reasonable during the first two to three years.

Repeated biochemical testing should also be performed as anterior pituitary deficiency may develop over time (and be a sign of a progressive underlying disease) or sometimes also resolve in case of hypophysitis [71].

Management of central diabetes insipidus

General management of DI by the specialist

In the majority of patients with central DI, osmoregulated thirst is intact, and therefore, oral

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fluid intake accurately compensates for urinary and insensible water losses. Even without treatment, patients are therefore typically eunatraemic. However, due to the typical symptoms of polyuria and polydipsia, usually treatment with desmopressin is started. Desmopressin is dosed empirically. To avoid the main adverse effect of hyponatraemia, the minimum desmopressin dose required to control symptoms should be started. The first dose is usually given at bedtime to initially reduce nocturia. If polyuria and polydipsia persist during the day, a daytime dose is added. Usually, this is a lifelong treatment since in most patients, DI is permanent. The exception is DI following neurosurgery, where it is mostly only transient, occurring within the first postoperative days and ceasing thereafter. Patients with DI after transsphenoidal surgery should therefore not receive a fixed dose of desmopressin, but instead their degree of polyuria must be observed carefully. If the polyuria becomes less pronounced or ceases, desmopressin can be tapered or withdrawn. If DI is still present 2 weeks after surgery, permanent DI becomes more likely.

Desmopressin can be administered intranasally, orally, subcutaneously or intravenously. Usually, start with an oral or intranasal preparation is recommended. A slightly lower risk of hyponatraemia has been reported upon treatment with the oral dose as compared to the intranasal dose. For the intranasal preparation, an initial dose of 10 mcg at bedtime can be titrated upward in 10 mcg increments. The usual daily maintenance dose is 10 to 20 mcg per day. The oral form has a lower potency than the nasal form because only about five per cent is absorbed from the gut. A 0.05 mg tablet is the equivalent of about 10 mcg of the nasal spray. For the oral preparation, the initial dose is therefore usually 0.05 mg at bedtime with titration upward until 0.1 mg to (max) 0.8 mg in divided doses. Table 2 shows the approximate equivalence doses of different applications (Table 2).

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, 2 mcg of desmopressin acetate may be given over two minutes; the duration of action is 12 h or more. The maximum dose of desmopressin required rarely exceeds 0.2 mg orally, 120 μg sublingually or 10 μg (one nasal spray) given 2–3 times daily. These doses usually produce plasma desmopressin levels higher than those required to cause maximum antidiuresis but reduce the need for more frequent treatment [72].

The major complication of desmopressin therapy is hyponatraemia. A retrospective review has shown that 27% of central DI patients show mild hyponatraemia on routine electrolyte testing and 15% develop more severe hyponatraemia, over long-term follow-up [73]. Hyponatraemia develops when the antidiuretic effects of desmopressin therapy prevent free water excretion, even with normal fluid intakes. This can be prevented by delaying doses of desmopressin to allow regular aquaresis, but regular electrolyte checks are recommended during initiation of therapy. Annual electrolyte checking is recommended for long-term follow-up, though more frequent monitoring is needed where hyponatraemia episodes are more frequent.

Management of DI for nonspecialists (with a focus on emergency management in hospitals)

Hypernatraemia is rare in ambulatory patients with DI; in contrast, the rate of hypernatraemia during hospital admission is clearly higher [73]. The aetiology of this hypernatraemia is multifactorial; if cognition is attenuated by critical illness, fluid intake may be reduced, and if the patient is vomiting, oral desmopressin intake is difficult. Most hospital studies report increased mortality in intensive care units associated with hypernatraemia [74], and it is a poor prognostic sign in patients who develop DI following head injury [75]. Recent observational data from a nationwide Swiss

Table 2. *Approximate equivalence doses of the different applications of desmopressin*

Application	i.v./s.c./i.m.	Intranasal	Per os	Sublingual
Concentration	4 μg/ml	0.1 mg/ml 10 μg/dosage	100/200ug tablets	60/120/240 μg tablets
Starting dosage	1 μg	10 μg	50 μg	60 μg

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cohort study showed an increased mortality rate in complex hypopituitary patients with central DI admitted to hospital, compared with hypopituitary patients without DI, consistent with vulnerability of DI patients to develop hypernatraemic dehydration in the context of severe illness [76]. The propensity to develop hypernatraemia during hospital admission is particularly marked in patients with adipsic DI [73], and this subgroup of DI patients have been documented to develop severe hypernatraemia [77], which may be complicated by thrombotic episodes [78].

Results of a retrospective audit of patients hospitalized with central DI showed that desmopressin treatment had been missed or delayed in 88% of admissions and that 35% of patients consequently developed dysnatraemia [79]. This was attributed to a lack of understanding of the critical nature of desmopressin amongst clinical staff [80]. Therefore, the Society for Endocrinology (SfE) in 2018 published guidelines on in-hospital management of central DI [81]. The results of these guidelines have generated a sensible basis for the management of DI when patients are admitted to hospital.

In hospitalized patients with only mild disease, who are alert and able to drink, complications should not be expected. In case of pneumonia or other respiratory complications, it may be advisable to prescribe oral rather than nasal desmopressin due to the limited absorption from congested nasal passages [82]. If patients have persistent fever and tachypnoea, insensible water losses are likely to be substantially increased; ordinarily, osmotically stimulated drinking should generate fluid intake sufficient to make up for insensible losses, but if cognitive function is impaired by fever, hypoxia or sepsis, intravenous fluids may be required.

In patients with severe illness, desmopressin should be given parenterally. The intravenous route is generally preferred because it obviates concerns about absorption and has the same total duration of action as the other parenteral routes. Prompt reduction in urine output should occur, and the antidiuretic effect generally lasts for 6 to 12 h. Urine osmolality and urine volume should be monitored to ascertain whether the dose was effective, and the plasma sodium measured at frequent intervals to ensure the improvement of hypernatraemia.

Patients with DI and severe dehydration should be treated with hypotonic fluids, either enterally (using water or milk) or, if necessary, intravenously (using 5% dextrose in water). Hypotonic fluids should be administered as an intravenous infusion, with the rate adjusted to exceed the hourly urine output and reverse the calculated total body water deficit. The usual aim is to provide just enough water to safely normalize serum sodium at a rate of < 0.5 mmol/L per h (<10–12 mmol/L per day) [83].

It is important to stress that, as hypernatraemic dehydration is associated with a hypercoagulable state, the risk of venous thrombosis, and pulmonary embolism, is substantial, particularly in an immobile patient [84]. It is therefore recommended to routinely prescribe prophylactic subcutaneous low molecular weight heparin during episodes of hypernatraemic dehydration, until eunatraemia is restored.

Nephrogenic DI is more difficult to treat since these patients have (at least partial) resistance to AVP agents. However, response to (sub)maximal dosed desmopressin treatment may be seen in some patients. If possible, the underlying disorder (e.g. hypercalcaemia) should be corrected. Patients should be instructed to take a low-sodium diet leading to modest hypovolaemia, which again stimulates isotonic proximal tubular reabsorption and thereby reduces solute delivery to the distal parts of the nephron.

Thiazide diuretics are sometimes efficient due to induced natriuresis, mainly if combined with a low-sodium diet. Nonsteroidal anti-inflammatory agents can also be used since they block prostaglandin synthesis, thereby increasing non-AVP-dependent water reabsorption.

Amiloride is the preferred drug to prevent progression or possibly improve lithium-induced DI in patients in whom lithium is continued.

So far, no reasonable medical therapeutic options can be offered to patients with primary polydipsia. These patients continue to be thirsty and to drink even in the presence of plasma osmolalities low enough to suppress AVP secretion, which may lead to severe complications such as water intoxication and severe electrolyte disturbances.

Summary and conclusion

After a detailed medical history and physical examination, a baseline laboratory assessment including

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confirmation of hypotonic polyuria and plasma sodium measurement is the first step in the differential diagnosis of polyuria–polydipsia syndrome. A low-sodium level points to PP, whereas an increased sodium level predicts DI. However, sodium levels are most commonly within the normal range, indicating the need for a subsequent stimulation test. Recently, osmotic (hypertonic saline) or nonosmotic (arginine) stimulation tests plus plasma copeptin measurement have replaced the indirect water deprivation test in the further evaluation of polyuria–polydipsia syndrome. If central DI is diagnosed, imaging studies are required to detect the aetiology of DI. In patients with idiopathic central DI, a close follow-up is needed since central DI can be the first sign of an underlying pathology. The management of central DI involves replacement of the free water deficit, with appropriate fluid intake, replacement of the deficient hormone AVP and treatment of the underlying condition, with a subsequent regular monitoring of therapy.

Conflict of interest

The authors report no conflicts of interest.

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