Received: 25 October 2022 | Revised: 10 December 2022 | Accepted: 29 December 2022

DOI: 10.1111/jne.13233

REVIEW ARTICLE

Journal of Neuroendocrinology WILEY

New developments and concepts in the diagnosis and management of diabetes insipidus (AVP-deficiency and resistance)

Anna Angelousi[1] | Krystallenia I. Alexandraki[2] | Chrysoula Mytareli[1] | Ashley B. Grossman[3,4,5] | Gregory Kaltsas[6]

[1]First Department of Internal Medicine, Unit of Endocrinology, Laikon Hospital, Athens, Greece

[2]Second Department of Surgery, Aretaieio Hospital Athens, Medical School, Athens, Greece

[3]Green Templeton College, University of Oxford, Oxford, UK

[4]Centre for Endocrinology, Barts and the London School of Medicine, London, UK

[5]NET Unit, Royal Free Hospital, London, UK

[6]First Department of Propaedeutic Internal Medicine, Laikon Hospital, National & Kapodistrian University of Athens, Athens, Greece

Correspondence
Anna Angelousi, First Department of Internal Medicine, Unit of Endocrinology, Laikon Hospital, National and Kapodistrian University of Athens, 17th Agiou Thoma Str, 11527, Goudi, Athens, Greece.
Email: a.angelousi@gmail.com

Abstract

Diabetes insipidus (DI) is a disorder characterised by the excretion of large amounts of hypotonic urine, with a prevalence of 1 per 25,000 population. Central DI (CDI), better now referred to as arginine vasopressin (AVP)-deficiency, is the most common form of DI resulting from deficiency of the hormone AVP from the pituitary. The less common nephrogenic DI (NDI) or AVP-resistance develops secondary to AVP resistance in the kidneys. The majority of causes of DI are acquired, with CDI developing when more than 80% of AVP-secreting neurons are damaged. Inherited/familial CDI causes account for approximately 1% of cases. Although the pathogenesis of NDI is unclear, more than 280 disease-causing mutations affecting the AVP2 protein or AVP V2 receptor, as well as in aquaporin 2 (AQP2), have been described. Although the cAMP/protein kinase A pathway remains the major regulatory pathway of AVP/AQP2 action, in vitro data have also revealed additional cAMP independent pathways of NDI pathogenesis. Diagnosing partial forms of DI, and distinguishing them from primary polydipsia, can be challenging, previously necessitating the use of the water deprivation test. However, measurements of circulating copeptin levels, especially after stimulation, are increasingly replacing the classical tests in clinical practice because of their ease of use and high sensitivity and specificity. The treatment of CDI relies on desmopressin administration, whereas NDI requires the management of any underlying diseases, removal of offending drugs and, in some cases, administration of diuretics. A better understanding of the pathophysiology of DI has led to novel evolving therapeutic agents that are under clinical trial.

KEYWORDS
aquaporin, desmopressin, diabetes insipidus, investigation, vasopressin

1 | INTRODUCTION

Diabetes insipidus (DI) is a rare nosological entity characterised by hypotonic polyuria and consequent polydipsia secondary to altered arginine vasopressin (AVP) hormone synthesis, action or dysregulation. The most common type is central DI (CDI) secondary to injury or dysfunction that affect AVP synthesis and/or secretion at the levels of the supraoptic or paraventricular nuclei (SON and PVN) and/or the superior portion of the supra-opticohypophyseal tract, as well as the hypothalamic osmoreceptors.[1,2] It has recently been proposed and generally accepted that the terms "AVP-deficiency" for CDI or "AVP-resistance" for nephrogenic DI (NDI) are more appropriate and less

confusing, and thus they should replace the current term DI,[3] although the classic term will be used in this text because most publications still use this terminology. NDI, or "AVP-resistance", is a less common form as a result of kidney resistance to normally secreted AVP. Both CDI and NDI need to be distinguished from primary polydipsia (PP), which occurs as a result of excessive water intake in the presence of normally-regulated AVP secretion and action. Gestational DI (GDI) is an even more rare form as a result of increased degradation of AVP by increased placental vasopressinase. A number of inherited causes of CDI and NDI have also emerged following the identification of novel mutations of genes involved in AVP synthesis or action, along with newly acquired and evolving pathologies of drug- or post-COVID-19-induced DI.[2,4–6]

The pathophysiology of DI is underpinned by a dysregulated water balance mechanism. AVP is the main regulator of water homeostasis, acting on the kidney through binding to the AVP V2 receptor (AVPR2) in the basolateral membrane of the collecting duct, resulting in an increased absorption of water and a subsequent increase in urine osmolality. Consequently, the diagnosis and differential diagnosis are based on clinical symptoms and biochemical alterations of serum and urinary sodium and osmolality levels, classically requiring the use of the water deprivation test[4] (but see below).

This systematic review aims to cover current and evolving knowledge of DI regarding its different aetiologies, the diagnostic tools employed, and its differential diagnosis and treatment, particularly because specific guidelines for DI are still under development. We will also critically discuss novel developments of the pathogenetic mechanisms and diagnostic tests, highlighting current gaps in molecular genetics, and emphasising areas for future preclinical and clinical research aimed at developing new therapeutic strategies.

2 | CAUSES AND CLASSIFICATION OF DI

2.1 | Classification of DI

2.1.1 | Central CDI

CDI results from AVP deficiency secondary to hypothalamic-pituitary (HP) pathologies, including both acquired and inherited causes **(Figure 1)**. The great majority of causes of DI are acquired, with CDI developing when more than 80% of AVP-secreting neurons are damaged, whereas inherited/familial CDI causes account for approximately 1% of cases[7,8] (Table 1). Inherited CDI may be a result of autosomal mutations in the arginine vasopressin-neurophysin II (*AVP-NPII*) gene, or X-linked recessive mechanisms.[9] Moreover, a rare form of CDI is adipsic CDI, which is associated with hypothalamic lesions in patients who have also lost their thirst sensation.

2.1.2 | NDI

NDI results from resistance to AVP at the kidneys that can be inherited or acquired. AVP is normally produced, but it is not recognised by the kidneys, leading to the production of dilute urine **(Figure 1).** In NDI plasma concentrations of AVP are characteristically elevated, mostly as a result of an acquired abnormality[10] (Table 1). Inherited NDI is rare, with an estimated incidence of approximately 1 per 1,000,000 population per year.[11] Approximately 90% of cases are X-linked, caused by mutations of the *arginine vasopressin receptor-2* (*AVPR2*) gene.[11] The remaining 10% are caused by mutations in the water channel protein *aquaporin-2* (*AQP2*) gene.[7]

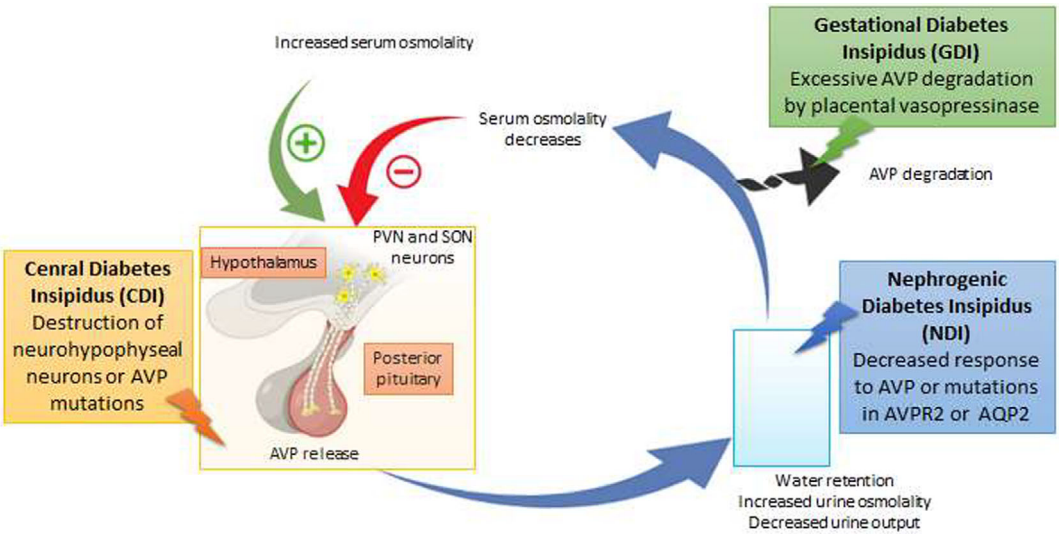

FIGURE 1 Different types of diabetes insipidus (DI). Central diabetes insipidus (CDI) results from inadequate production and/or secretion of arginine vasopressin (AVP) in the hypothalamic–neurohypophyseal system in response to osmotic stimulation caused either by disruption of the neurohypophysis (acquired form) or by mutations in AVP (hereditary). Nephrogenic DI (NDI) results of an inadequate response of the kidneys to AVP, either acquired (as a result of drugs or electrolyte disorders) or hereditary (as a result of mutations in AVP receptor 2 [AVPR2] or the water channel aquaporin 2 [AQP2] genes). Gestational DI (GDI) caused by increased activity of arginine vasopressinase reduces the levels of AVP leading to a presentation similar to that of CDI. Abbreviations: PVN, paraventricular nuclei; SON, supraoptic nuclei.

TABLE 1 The causes of the different types of diabetes insipidus (DI)

Types of DI	Causes
Central DI	Hereditary (1% of CDI cases) • Autosomal dominant familial DI (mutation of the AVP gene) • Autosomal recessive mutation (p.Pro26Leu) (region between the *AVP* and *OXT* gene • Wolfram syndrome type 1 as a result of *WFS1* or rarely to *CISD2* mutation • Congenital hypopituitarism • Septo-optic dysplasia • Other rare syndromes Schinzel-Giedion syndrome Culler-Jones syndrome Alstrom syndrome Hartsfield syndrome Webb-Dattani syndrome PMSE syndrome (polyhydramnios, megalencephaly and symptomatic epilepsy) Acquired (99% of CDI cases) • Post-operative (iatrogenic-intracranial and endoscopic transsphenoidal surgery) (20% of CDI cases)/trauma or post-radiotherapy (16% of CDI cases) • Idiopathic or autoimmune (including lymphocytic hypophysitis, xanthomatous hypophysitis, granulomatous hypophysitis, IgG4-related hypophysitis, anti-vasopressin neuron antibodies) (30%–50% of non-traumatic CDI cases) • Neoplastic disease Metastases (breast, lung cancer lymphoma) (5% of CDI cases) Craniopharyngioma, meningioma, germinoma, Rathke's cleft cyst, astrocytoma Hematological malignancies (leukaemia, lymphoma) • Infiltrative diseases Neurosarcoidosis Langerhans cell histiocytosis (of monoclonal origin) Granulomatous hypophysitis Erdheim-Chester disease • Anorexia nervosa • Infectious Meningitis Encephalitis SARS-CoV2 Tuberculosis Abscess • Vascular Hypothalamic/pituitary/cerebral infarction or haemorrhage, Sheehan syndrome, aneurysm • Drugs (see also Table 3) • ICIs: ipilimumab, nivolumab, avelumab, tremelimumab, durvalumab, sintilimab, atezolizumab • Others: phenytoin, ethanol, temozolomide
Nephrogenic DI	Hereditary (incidence 1 per 1,000,000) • More than 280 X-linked recessively inherited mutations in *AVPR2* (90% of cases) including a large deletion including the whole loss of *AVPR2* and part of the *ARHGAP4* • Autosomal dominant or recessive inherited mutations in *AQP2* (10% of cases) Acquired Electrolyte abnormalities • Hypercalcaemia • Hypokalaemia Kidney diseases • bilateral urinary tract obstruction • autosomal dominant polycystic kidney disease • medullary cystic kidney disease, • renal amyloidosis • Sjogren syndrome • renal infarction Drugs (see also Table 3) • Lithium • Antibiotics (penicillins, tetracyclines, aminoglycosides, antifungal) • Anti-CMV (foscarnet and cidofovir) • Antiretroviral Bartter syndrome • *MAGED2*, *SLC12A1* and *KCNJ1* mutations Hematological • Multiple myeloma • Amyloidosis • Sickle cell disease
Gestational DI	Increased AVP degradation (high activity of placental vasopressinase) (incidence 2–4 per 100,000 cases)

Abbreviations: Anti-CMV, anti-cytomegalovirus; AVP, arginine vasopressin; CDI, central DI; CISD2, CDGSH iron sulfur domain 2 gene; ICIs, immune check point inhibitors; Ig, immunoglobulin; *KCNJ1*, potassium inwardly rectifying channel subfamily J member 1; MAGED2, MAGE family member D2; OXT, oxytocin/neurophysin I prepropeptide; PCSK1, proprotein convertase subtilisin/kexin-type 1 gene; SAS, somatostatin analogues; SLC12A1, electroneutral solute carrier family 12A1; WFS1, Wolframin syndrome gene.

2.1.3 | GDI

GDI is rare, encountered in 2–4 per 100,000 pregnancies, occurring during the third trimester of pregnancy, and usually resolving 4–6 weeks after delivery[7,10] (Figure 1). Any form of CDI can be exacerbated or first become apparent during pregnancy because AVP degradation is increased by the enzyme vasopressinase expressed by placental trophoblasts.[4,12,13] This enzyme can be detected at 10 weeks of gestation and increases by approximately 300-fold throughout pregnancy.[13] GDI presents with newly developed polyuria and polydipsia, but may remain undiagnosed as polyuria is attributed to increased maternal plasma volume.[14] Human chorionic

gonadotropin (βhCG) also plays an additional role in increasing maternal plasma volume because it reduces the thirst threshold, whereas the physiological hypertrophy and hyperplasia of the anterior pituitary may compress the posterior pituitary resulting in decreased AVP release.[13] GDI may be precipitated by liver dysfunction because degradation of endogenous vasopressinase may be reduced. GDI can lead to pregnancy-related complications, increasing the risk of pre-eclampsia.[15]

2.2 | Causes of CDI

2.2.1 | Neurosurgery or trauma

The pituitary gland, pituitary stalk and hypothalamus are relatively vulnerable to injury from head trauma and surgical interventions. Minimally-invasive surgery such as endoscopic transsphenoidal surgery (eTSS) carries a lower risk of post-operative DI compared to more extensive procedures[7,8] (Table 2). Post-operative DI may be transient or permanent and of variable severity. New-onset post-operative DI was found in 27.8% of patients with non-adenomatous sellar/parasellar lesions undergoing eTSS.[16] The incidence of CDI after eTSS removal of pituitary adenomas limited to the sella varies from 11% to 22%, whereas, in very large tumours, it can occur in up to 60%–80% of cases, being transient in 1%–4%.[16,17] A new diagnosis of post-operative CDI was made in 7.5% of 160 patients with non-functioning pituitary adenomas (NFPAs) undergoing initial eTSS, being permanent in only 2.5.%.[18] In a larger retrospective study including 333 patients with NFPAs, post-operative DI occurred in 21.7% of patients undergoing initial TSS, being permanent in 2 (0.6%).[19]

2.2.2 | Benign or malignant neoplasms of the hypothalamic-pituitary region

Although pituitary adenomas account for 90% of all sellar/parasellar lesions, they seldom produce DI even when relatively large.[16] In one recent study, only 0.6% of 160 patients (i.e., a single patient) with NFPAs presented with pre-operative CDI.[18] The most common pathologies of sellar/parasellar lesions presenting with CDI are non-adenomatous lesions, whereas the highest prevalence of CDI was found in less commonly encountered pathologies such as germ-cell tumours (76.7%).[20] Craniopharyngiomas and Rathke's cleft cyst represented 23.4% and 12.7% respectively of all sellar/parasellar lesions, with craniopharyngioma being the most common cause of CDI in children, and encountered in 25%.[10,21] The high incidence of CDI in craniopharyngiomas may be related to their embryological origin from the remnants of Rathke's pouch, as well as the more aggressive surgical approaches utilised, and usually persists after surgery.[4]

Myelodysplastic syndromes and haematological malignancies can also involve the HP-region leading to CDI.[22] Approximately 5% of patients with known malignancy have "latent" CDI.[23] Pituitary metastases are found in 1% in autopsy series, and in 0.14%–28.1% of all brain metastases, mostly in patients with extensive disease, with lung, breast and myeloma being the most common primary sites[16,24–26] (Table 1). In a recent series of patients with pituitary metastases, the prevalence of CDI varied between 27% and 70%.[16]

2.2.3 | Systemic and/or infiltrative disorders

Other mostly non-neoplastic pathologies include lymphocytic hypophysitis, Langerhans cell histiocystosis (LCH), abscesses and neurosarcoidosis.[16,27] Additional infiltrative disorders include granulomatosis with polyangiitis,[28] and immunoglobulin (Ig)G4-related hypophysitis.[29,30] Most of these cases also present with concomitant anterior pituitary hormonal deficiencies.[16] Up to 40% of patients with LCH develop CDI, particularly in the presence of multisystem involvement.[31,32] It is estimated that approximately 2% of patients with neurosarcoidosis will develop symptoms of CDI.[31]

2.2.4 | Drug-induced CDI

Both phenytoin and ethanol exert a transient inhibitory effect on AVP release, causing transient CDI.[33–35] Temozolomide, an oral DNA-alkylating chemotherapeutic agent, has also been associated with impaired AVP and oxytocin release.[36,37] Similarly, ketamine is also known to inhibit glutamate-stimulated AVP release from the neurohypophysis.[38,39] Aminoglycosides can cause both CDI and NDI.[40–42] The role of opioids in the pathogenesis of DI was described more than 20 years ago, through inhibition of AVP release from the neurohypophysis, especially when AVP is initially

TABLE 2 Grading of pituitary or sellar/parasellar post-operative-induced diabetes insipidus (DI)

Grades	Post-operative DI	Complications
0	Unlikely DI	Probably physiological or osmotic polyuria (no sequelae)
1	Probable transient DI	Spontaneous resolution within 48 h after surgery
2	Transient DI	-Treatment with desmopressin for < 2 weeks after surgery -May prolong length of hospital stay (Clavien-Dindo class II).
3	Prolonged DI	Treatment for a minimum of 2 weeks, but fewer than 6 months (Clavien-Dindo class II).
4	Chronic (persisting) DI	Treatment for more than 6 months (Clavien-Dindo class II)

TABLE 3 Drug-induced diabetes insipidus (DI) and their mechanisms of action

Drugs	Type of DI	Category of drug	Mechanisms
Lithium[11,44,45]	NDI	Drug for bipolar disorders	-Lithium inhibits adenyl cyclase at the distal renal tubule and collecting duct decreasing cAMP and PKA stimulation resulting in AQP2 downregulation -Lithium-associated hypercalcaemia may potentially increase the risk of NDI
Antibiotics			
Demeclocycline[41]	NDI	Tetracycline derivative antibiotic	-Demeclocycline enters in the renal collecting duct through transporter channels hoat1 and hoat3, located on the basolateral membrane and inhibits AVP-induced water flow -The mechanism of affecting the AVP and AQP2 signalling cascade is unknown
Amphotericin B[41]	NDI	Antifungal antibiotic	Amphotericin B creates pores in cell membranes inducing hypokalaemia and inhibiting Gsα proteins and/or adenylate cyclase resulting in AQP2 downregulation
Aminoglycosides[41]	NDI + CDI	Antibiotics	-Ifosfamide and its metabolites, such as chloroethylamine and monoamino-oxidase induces CNS toxicity including also hypothalamus and/or pituitary gland without crossing the blood–brain barrier -Bartter-like syndrome by CaSR stimulation
Sulfamethoxazole-trimethoprim (SMX)[46]	NDI	Antibiotics	-SMX induces interstitial nephritis; the mechanism leading to NDI is unclear -It is also probably related to trafficking defects and/or AQP2 downregulation
Pencillin (ofloxacin, methicillin)[47,48]	NDI	Penicillin antibiotics	Acute interstitial nephritis; the mechanism leading to NDI is unclear
Foscarnet[49]	NDI	Antiviral agents	Renal tubular acidosis; the mechanism leading to NDI is unclear
Tenofovir disoproxil fumarate and didanosine[50,51]	NDI	Antiretroviral drug	-Tubulointerstitial nephropathies; the mechanism leading to NDI is unclear -Tenofovir was mainly associated with proximal tubular dysfunction, overt Fanconi's syndrome, and NDI in 12.5% of cases
Others			
Ketamine propofol, dexmedetomidine, sevoflurane[52,53]	CDI	Anaesthetic drugs	Ketamine's antagonist action on *N*-methyl-D-aspartate receptors, resulting in inhibition of glutamate-stimulated AVP release from the neurohypophysis
Phenytoin[41,43]	CDI	Anti-epileptic drugs	Transient inhibition of AVP
Ethanol[43]	CDI + NDI		Transient inhibition of AVP
Temozolomide (TMZ)[46,54,55]	CDI	Oral DNA-alkylating agent	Disruption of actin cytoskeleton in neuroendocrine cells, and modification of purinergic receptor signaling in magnocellular neurons of the supraoptic nucleus by TMZ, resulting in an impairment of oxytocin and AVP release
Somatostatin analogs[56]	CDI and NDI	Somatostatin receptors inibitors	Inhibition of AVP release from the pituitary and disrupted of AVP action at distal nephrons
Opioids[57,58]	CDI	Morphine, other opiates	Inhibition of AVP secretion acting on the hypothalamic-neurohypophyseal axis
ICIs[59–73]			
-Ipilimumab -Nivolumab	CDI	CTLA4/PD-1inhibitors	Autoimmunity, hypothalamitis and/or-posterior pituitary

(Continues)

TABLE 3 (Continued)

Drugs	Type of DI	Category of drug	Mechanisms
-Avelumab -Atelizumab -Ipilimumab + Nivolumab -Tremelimumab + Durvalumab -Sintilimab			

Abbreviations: AQP2, aquaporine-2; AVP, arginine-vassopressine; CaSR, calcium-sensing receptors; CDI, central DI; CNS, central neural system; CTLA4, cytotoxic T-lymphocyte-associated protein 4; ICIs, immune check point inhibitors; NDI, nephrogenic DI; PD-1, programmed cell-death protein 1; PKA, protein kinase A; TMZ, temozolomide.

stimulated by an osmotic stimulus.[43] Somatostatin analogues can also cause both CDI and NDI, especially when administered at high doses. These data are shown in Table 3. However, this is unlikely to be clinically important.

2.2.5 | Idiopathic CDI

Approximately 30% of the non-traumatic cases of CDI are idiopathic, secondary to the destruction of the AVP-secreting cells in the hypothalamic nuclei,[4] probably via an autoimmune process in the majority of cases.[54]

2.2.6 | Anorexia nervosa

AVP release is often disturbed in patients with anorexia nervosa, but, when polyuria occurs, it is relatively mild and mostly because of a primary increase in thirst, possibly a form of psychogenic polydipsia.[54]

2.3 | Evolving aetiologies

2.3.1 | Post-COVID-19 CDI

SARS-CoV-2 infection can directly target hypothalamic and pituitary tissues because of the high expression of angiotensin-converting enzyme 2 receptors at these sites.[52,53] Coronavirus-induced hypoxaemia and the subsequent "cytokine storm" may also contribute to damage in these areas.[74] Currently, there are few published reports of COVID-19 infection-related CDI.[52,53,74–76] However, the paucity of reports suggest that, even if this phenomenon exists, it is exceedingly rare.

2.3.2 | Immune check point inhibitors (ICIs)

Patients treated with ICI rarely develop CDI secondary to an autoimmune process involving the hypothalamic-posterior pituitary region. Currently, only 11 case reports with ICI-induced CDI have been described. Almost all patients developed CDI with a substantial delay from treatment administration, ranging from 28 to 270 days.[56–60,77–82] Nine of the 11 patients suffered from solid malignancies, with CDI presenting as excessive polyuria. However, the diagnosis in many cases remains unclear; in the majority of these cases, the diagnosis of CDI was based on the presence of polyuria/polydipsia, plasma or urine osmolality levels and/or electrolytical disturbances without confirmation by dynamic tests or the measurement of copeptin levels.[56,57,59,77,79,82] In five patients, CDI developed in the context of panhypophysitis,[57–60,79] whereas, in a further five,[56,77,78,80,82] it was secondary to isolated damage to the posterior pituitary, and, in one case, it was considered to be a result of hypothalamitis.[81] Patients treated with anti-PD1/PD-L1 agents commonly develop isolated injury of the posterior pituitary, without concomitant anterior pituitary injury, whereas, in patients treated with anti-CTLA4 agents, CDI was always associated with panhypophysitis (Table 3).

3 | PATHOGENESIS AND MOLECULAR GENETICS OF DI

Autosomal dominant mutations of the *AVP* gene are the most common genetic causes of CDI, whereas autosomal recessive inheritance is described only in anecdotal cases.[61,62] All of these mutants impair AVP binding to the V2 receptor[63] (**Figure 2**). Congenital nephrogenic DI (cNDI) results from mutations leading to loss of function of the AVPR2 or AQP2, leading to variable degrees of resistance to AVP.[64,65] These mutations include deletions, insertions or even missense pathogenic variants of the *AVPR2* (Figure 2). The binding of AVP to AVPR2 activates adenylyl cyclase, increasing intracellular cAMP levels and activating cAMP-dependent protein kinase A (PKA).[66] Activation of AVPR2 by AVP binding ultimately leads to the translocation of AQP2 to the apical surface of the cells in the collecting duct of the kidney, thereby increasing water reabsorption and urine osmolality[66] (Figure 3). The short-term regulation of AQP2 by AVP involves the movement of AQP2 from the intracellular vesicles to the luminal membrane, whereas, for long-term regulation, which requires a sustained elevation of circulating AVP for more than 24 h, there is an increase

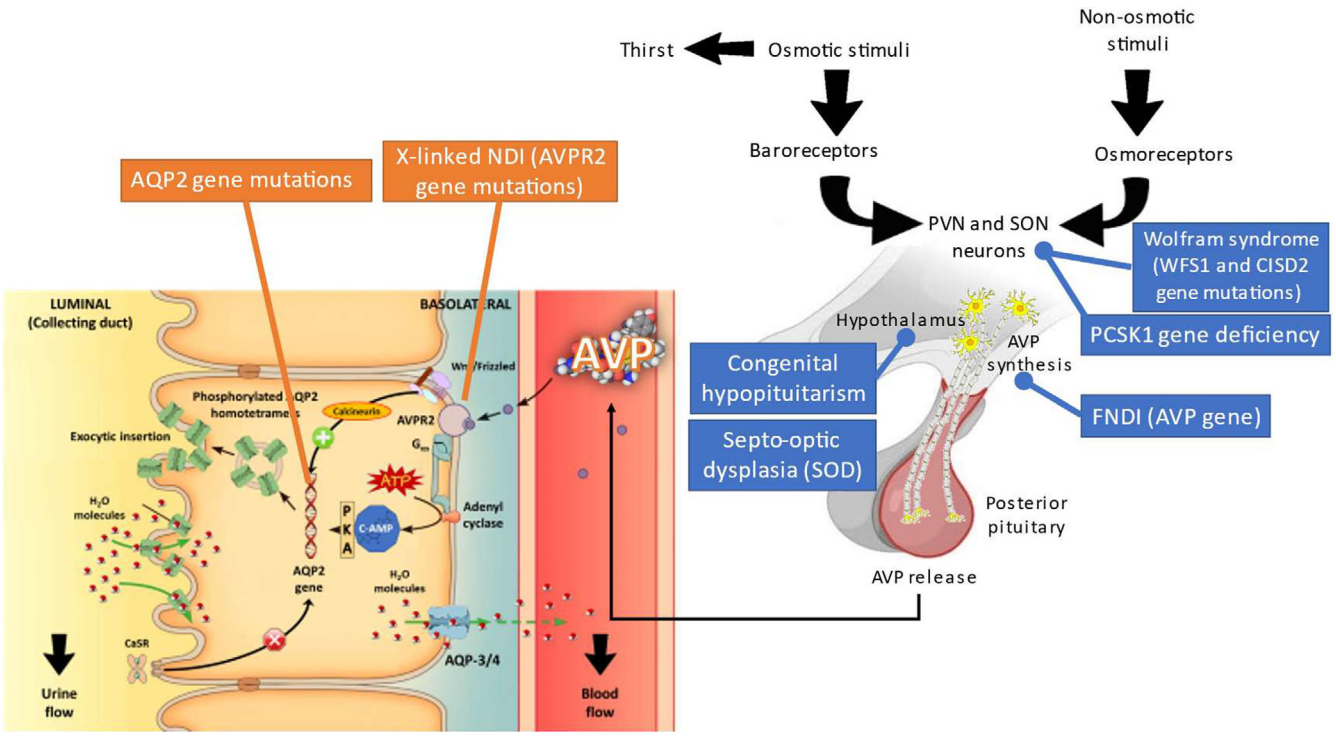

FIGURE 2 Pathogenesis and genetic background of diabetes insipidus (DI). Familial central diabetes insipidus (CDI) is caused by mutations of the gene encoding arginine vasopressin (AVP) (also called familial neurohypophysealn DI [FNDI]). Autosomal dominant familial CDI mutations are the most common leading to retention of the mutant AVP prohormone in the endoplasmic reticulum (ER) of magnocellular neurons. Mutant AVP, and functional AVP protein that is produced from the non-affected allele, form high-molecular weight complexes that are destined for ubiquitylation and proteasomal degradation by the ER quality control pathway. These mutants impair AVP binding to the V2 receptor and thus diminish adenylate cyclase activity which leads to the stimulation of the protein kinase (PKA) pathway, which activates aquaporin 2 (AQP2) transcription and translocation in the principal cell of the collective duct (64). Autosomal recessive inheritance is described only in anecdotal cases and is a result of missense variations or deletions (62,63). Congenital nephrogenic DI (cNDI) results from mutations leading to loss of function of the AVP receptor 1 (AVPR1) and AVP receptor 2 (AVPR2) or AQP2 leading to variable degrees of resistance to AVP (65,66). Mutations in AQP2 gene cause autosomal recessive or dominant NDI (93). Other familial syndromes include: (1) Wolfram syndrome type 1 (WFS1) gene inherited as an autosomal recessive in which CDI is a result of a loss of AVP -secreting neurons in the SON and impaired processing of AVP precursors. More than 300 mutations responsible for Wolfram syndrome (WFS) cases have been identified, with the majority of them located in exon 8 encoding the nine transmembrane segments and the C-terminal tail of wolframin (72,73). Recently, another rare causative gene with autosomal-recessive inheritance, CISD2, has been identified in patients with Wolfram syndrome type 2 (WS2) resulting in early optic atrophy, diabetes mellitus, deafness and a decreased lifespan, but not DI. Isolated neurohypophyseal CDI associated with compound heterozygous mutations in the WFS1 gene has been also described. In autosomal dominant neuro-hypophyseal DI, the mechanism by which dominant mutants cause neuronal remains unclear. (2) Proprotein convertase subtilisin/kexin-type 1 (PCSK1) gene deficiency leads to deficiency of the pre-pro-PC1/precursor 3 for which activation is involved in the processing of numerous hypothalamic pro-hormones, including AVP. (3) Septo-optic dysplasia (SOD) is a highly heterogeneous condition with phenotypes that include midline and forebrain abnormalities, as well as optic nerve and pituitary hypoplasia, in which affected patients may have abnormal thirst as well as a defect in AVP release (76). Mutations in genes involved in developmental transcription factors, such as HESX1 essential for normal forebrain/pituitary development have been described (75). PVN, paraventricular nuclei; SON, supraaortic nucleus

in the abundance of water channels. In the absence of AVP stimulation, collecting duct epithelia exhibit very low permeability to sodium, urea or water (Figure 3).[66]

High concentrations of urinary calcium levels counteract AVP action via the activation of the calcium-sensing receptor, which is expressed in the luminal membrane of collecting duct cells, impairing AQP2 trafficking. In vitro studies have shown that Wnt5a regulates AQP2 protein expression, phosphorylation and trafficking, and may increase the apical membrane localisation of AQP2 and urine osmolality in an NDI mouse model. This finding suggests that Wnt5a is an endogenous ligand directly regulating AQP2 independently of the classical AVP/cAMP signalling pathway.[67,68] Furthermore, calcineurin has been shown in vitro to regulate Wnt5a-induced AQP2 activation without affecting intracellular cAMP-PKA activity, whereas its activator, arachidonic acid, also demonstrates a vasopressin-like effect[68] (Figure 3).

3.1 | CDI

3.1.1 | Congenital CDI

Hereditary DI is transmitted both as autosomal dominant and X-linked.[63,69] A number of familial and congenital diseases have been

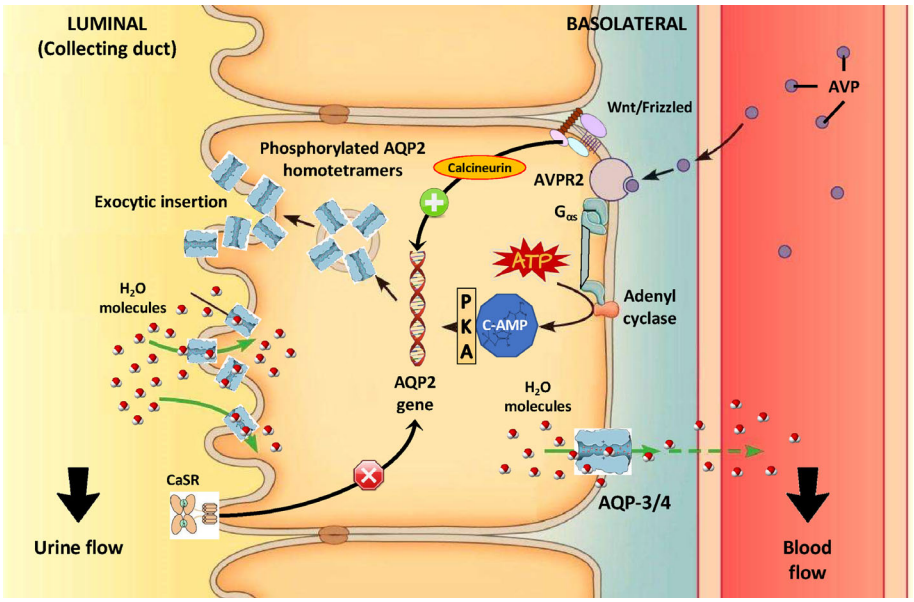

FIGURE 3 Mechanisms of the water transport in the principal cells of the collecting duct. The anti-diuretic effect of arginine vasopressin (AVP) is mediated via its binding to the V2 receptor (AVPR2) – a G protein- transmembrane receptor coupling to the stimulatory G protein a (Gs) – located in the basolateral membrane of the principal cell. This binding activates the adenylate cyclase, which converts ATP to cAMP and subsequently leads to the activation of the protein kinase A (PKA) pathway. PKA induces the phosphorylation of the aquaporin 2 (AQP2), resulting in the formation of P-AQP2 homotetramers. The phosphorylated homotetramer is inserted into the apical membrane and facilitates water transport from the urine into the cell. In addition, PKA also increases AQP2 transcription by activating nuclear factors. At the basolateral membrane, water leaves the cell via aquaporins 3 and 4 (AQP3 and AQP4), whereas, at the apical membrane, the P-AQP2 homotetramer is dephosphorylated and recycled into the cytosol where it dissociates into homomers. High concentrations of urinary calcium counteract AVP action via the activation of the calciumsensing receptor (CaSR) that is expressed in the luminal membrane of collecting duct cells, impairing the trafficking AQP2 via Wnt5a, an endogenous ligand that can regulate directly AQP2 independently of the intracellular pathway of the AVP/cAMP signaling pathway. Furthermore, calcineurin has been shown in vitro to regulate Wnt5a-induced AQP2 activation without affecting intracellular cAMP-PKA activity

associated with CDI such as familial CDI, Wolfram syndrome, congenital hypopituitarism and septo-optic dysplasia (**Figure 2**).

Familial CDI

Familial CDI is caused by mutations of the gene encoding AVP, and it is also called familial neuro-hypophyseal DI (FNDI) (MIM 125700).[63] FNDI is a rare disorder accounting for only 1% of CDI cases (Figure 2). Autosomal dominant familial CDI mutations are the most common, leading to retention of the mutant AVP prohormone in the endoplasmic reticulum of magnocellular neurons.[63] Autosomal recessive inheritance is described only in anecdotal cases. Some rare hereditary syndromes manifesting with CDI are summarised in Table 1.

Wolfram syndrome type 1

CDI occurs in approximately 70% of patients of this syndrome, and all four related disorders (diabetes mellitus, optic atrophy and deafness) are present in almost 50% of patients.[7] CDI is the result of a loss of vasopressin-secreting neurons in the SON and impaired processing of vasopressin precursors (**Figure 2**). It is inherited as an autosomal recessive trait with incomplete penetrance and is caused by at least two different genes: *WFS1* and *CISD2*.[70] Mutations of the *WFS1* gene are responsible for most WFS cases, with more than 300 different mutations being identified.[83,84] Recently, another rare causative gene with autosomal-recessive inheritance, *CISD2*, has been identified in patients with Wolfram syndrome type 2, resulting in early optic atrophy, diabetes mellitus, deafness and decreased lifespan, but not DI.

Congenital hypopituitarism

CDI has been described in patients with congenital hypopituitarism with or without ectopia of the posterior pituitary lobe.[85] The defects in posterior pituitary function include reduced AVP release after osmotic challenge leading to symptomatic CDI, nocturia, plus hypodipsia or polydipsia.

Septo-optic dysplasia (SOD)

SOD is a highly heterogeneous condition with phenotypes that include midline and forebrain abnormalities, as well as optic nerve and pituitary hypoplasia. Most cases of SOD are sporadic, but familial cases have been described in association with mutations in genes involved in developmental transcription factors, such as HESX1, which are essential for normal forebrain/pituitary development.[86] Affected patients may have abnormal thirst, as well as a defect in AVP release.[87]

3.1.2 | Acquired CDI

Neurosurgery or trauma

Several factors have been described as predictors of CDI following TSS including younger patient age, larger tumour size and the absence

of the "bright spot" of the posterior pituitary in pre-operative T1-weighted magnetic resonance imaging (MRI).[19] Transient CDI typically occurs within 24–48 h after surgery and resolves during the next 2 weeks[88] (Table 2). Post-operative CDI may also occur in combination with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in the triphasic response.[88] Damaged AVP-containing neurons cause immediate transient DI, followed by SIADH as the injured neurons of the hypothalamic-posterior pituitary tract degenerate and release all their stored vasopressin.[88] This is followed by permanent post-operative DI typically manifesting 5–8 days after surgery.[89]

Post-operative serum sodium levels can be predictive of CDI duration; sodium levels > 145 mmol L^{-1} within the first 5 post-operative days exhibit a high predictive value for the development of permanent CDI, whereas patients with sodium levels <145 mmol L^{-1} rarely, if ever, develop permanent CDI.[89] Severe damage to the hypothalamus by neurosurgery or trauma often results in the typical triphasic (DI-SIADH-DI) response; permanent CDI develops after the posterior pituitary stores are depleted.[90] One of the largest studies including 1571 patients with pituitary adenomas who underwent eTSS showed that 31% of patients developed immediate post-operative polyuria, 17% had polyuria on day 3 and 6% had polyuria on day 7; transient polyuria developed in 3.4% of patients followed by transient hyponatraemia, whereas only 1.1% exhibited the classic triphasic pattern of polyuria, hyponatraemia and then polyuria (2 3). In a smaller study including 474 patients undergoing eTSS, CDI was found in 25%, being transient DI in 19% and permanent in 6%.[88,91]

Idiopathic CDI

It has been suggested that an autoimmune process is involved in many patients with idiopathic CDI.[54] A longitudinal prospective study evaluated the presence of cytoplasmic antibodies against vasopressin cells in 858 patients with endocrine autoimmune diseases without clinically overt CDI.[92] Nine patients were found to have AVPc antibodies (AVPcAb) at study enrollment, and were prospectively followed for 4 years along with 139 AVPcAb-negative patients who acted as a control group. Five of these nine AVPcAb-positive patients had normal posterior pituitary function at study entry, based on water deprivation testing. However, during follow-up, three developed partial CDI and one developed complete CDI, whereas one retained normal posterior pituitary function. The remaining four patients, albeit asymptomatic at study entry, all demonstrated partial CDI following a water deprivation test. In another study of 150 patients with CDI, AVPcAbs were found in 21 patients with apparent idiopathic disease and in 14 patients with non-idiopathic disease including cases of granulomatosis, cranial trauma, post-surgery and tumours.[93] The occurrence of AVPcAbs was independently correlated with age < 30 years at disease onset in those with idiopathic CDI, a history of autoimmune disease or pituitary stalk thickening.[93]

Lymphocytic infundibulo-neurohypophysitis (LINH) accounts for a substantial subset of autoimmune CDI, and is characterised by lymphocytic infiltration of the posterior pituitary and infundibular stalk, thus reducing the production and release of AVP. Rabphilin-3A, a regulator of secretory vesicle trafficking, was found to be expressed in the posterior pituitary and hypothalamic vasopressin neurons, but not the anterior pituitary, and autoantibodies to rabphilin-3A were the most common auto-antibodies found in LINH.[94] Thus, autoantibodies to rabphilin-3A may serve as a biomarker for the diagnosis of LINH, and consequently may be also a useful marker for the differential diagnosis in patients with CDI.

Hypoxic encephalopathy

Hypoxic encephalopathy or severe ischaemia can lead to diminished AVP release from the SON.[95] Beyond this mechanism, a recent in vitro study has shown that *Lgals3*, a microglial activation-related gene, plays an important role in the elimination of AVP neurons by inducing phagocytic activity of the microglia after hypothalamic injury, and thus may also be implicated in AVP deficiency.[96]

Adipsic CDI

Adipsic CDI is a particular and rare form of CDI caused by hypothalamic damage presenting as a complication after extensive surgery or systemic or infiltrative disease. It may be also caused by neurosurgical clipping of anterior communicating artery aneurysms. Recovery of thirst is unusual.[88,97] These patients do not feel an urge to compensate for the fluid loss by drinking water, and are rendered at high risk of hypernatraemia and severe dehydration.

Systemic and infiltrative diseases

Hypothalamic-pituitary involvement in neurosarcoidosis is often asymptomatic, although, occasionally, it may be the first manifestation of sarcoidosis (< 5% of cases).[97] Granuloma formation affecting the hypothalamic-pituitary-axis may lead to irreversible damage and hormonal deficiencies, and can also lead to the loss of thirst sensation, thus causing adipsic CDI. Polyuria in patients with sarcoidosis may also be a result of NDI, induced by hypercalcaemia.

Metastases

DI develops in up to 70% of patients with metastatic disease in the pituitary, either as the only manifestation of pituitary involvement or in association with anterior pituitary deficiencies. In a recent study of 11 patients with pituitary metastases, the most common clinical presentations were panhypopituitarism (27.7%) and CDI (27.7%–70%).[98] Breast (37.2%) and lung (24.2%) cancers are the most common primary malignancies, followed by the prostate (5%), kidney (5%) and lymphomas.[98] This is related to the different vascularisation of the posterior pituitary because it is supplied from the inferior hypophyseal artery in contrast to the anterior pituitary that is supplied by the hypophyseal portal system. Moreover, because of the smaller size of the posterior pituitary region, the same volume of metastatic tissue may produce earlier symptoms compared to anterior pituitary involvement.[98]

ICI-induced CDI

The mechanistic basis of ICI-induced CDI remains unclear, but includes type II and type IV hypersensitivity reactions, as well as

ectopic pituitary CTLA-4 expression.[79,99] PD-1 may be expressed in pituitary cells or lymphocytes, whereas PD-L1 is also expressed in pituitary adenomas.[56–59,77,78,82,100–102] Because these antibodies are of the IgG4 isotype, the mechanism of IgG4-related hypophysitis may be related to that of anti-PD-1/PD-L1-related hypophysitis[78] (Table 3).

3.2 | NDI

3.2.1 | cNDI

cNDI results from mutations leading to loss of function of AVPR2, or the water channel AQP2, leading to variable degrees of resistance to AVP[64,65] cNDI exclusively affects males because *AVPR2* is located on the X chromosome (Xq-28) (**Figure 2**). Activation of the V1 receptor induces vasoconstriction and enhancement of prostaglandin release, whereas the V2 receptors mediate the antidiuretic response as well as peripheral vasodilatation and the release of factors VIIIc and von Willebrand factor from endothelial cells.[65] Mutations of *AVPR2* (MIM*300538) account for over 90% of cNDI cases.[63,65]

To date, more than 280 disease-causing variants have been identified affecting different parts of the receptor protein, with considerable phenotypic variability. Missense mutations, small insertions and deletions account for around 90% of *AVPR2* alterations.[65] Approximately half (55.8%) of the reported *AVPR2* mutations are missense, whereas the remainder comprise nonsense mutations and small frameshift deletions.[66] Missense mutations can lead to partial preserved receptor expression and function, and hence a milder cNDI phenotype. Large deletions of the *AVPR2* gene causing X-linked cNDI have also been reported, resulting in a spectrum of disease phenotypes depending on the size and extent of the deletion.[103] Loss-of-function mutations lead to more severe phenotypes.[66]

Mutations in *AQP2* (MIM*107777) account for the remaining 10% of cases of NDI, causing autosomal recessive or dominant NDI (MIM#125800).[103] To date, approximately 48 putative disease-causing *AQP2* mutations have been identified.[104]

Large deletions leading to complete loss of the whole *AVPR2* and parts of the neighbouring gene *ARHGAP4* have been also recently identified, leading to a X-linked cNDI.[65,105–107] The *ARHGAP4* (MIM*300023) gene encodes a GTPase activating protein-4 named Rho that is also considered to play a role in lymphocyte differentiation in haematopoietic cells.

3.2.2 | Acquired NDI

Hypercalcaemia

A renal concentrating defect may become clinically apparent if the plasma calcium concentration is persistently above 11 mg dL^{-1} (2.75 mmol L^{-1}) leading to a reduction of sodium chloride reabsorption, thereby interfering with the ability of AVP to increase collecting tubule water permeability.[15] By reducing calcium and sodium reabsorption in the loop of Henle, hypercalcaemia is associated with an increase in calcium delivery to the luminal calcium-sensing receptors that reduce AVP-induced increases in water permeability. Hypercalcaemia may also impair water reabsorption by autophagic degradation of AQP2.[108]

Hypokalaemia

Persistent severe hypokalaemia, with serum potassium concentration < 3 mmol L^{-1}, can also impair urinary concentrating ability by decreasing collecting tubule responsiveness to AVP mediated by decreased expression of AQP2. In addition, both hypokalaemia and hypercalcaemia also induce diminished sodium chloride reabsorption at the thick ascending limb, reducing further AVP-induced increase in water permeability.[109] Down-regulation of urea transporters may also contribute to the impairment of urinary concentrating ability. In addition, enhanced autophagic degradation AQP2 has been demonstrated to be an early event in hypokalaemia-induced NDI.[109]

Renal diseases

Symptomatic NDI can develop in a variety of kidney diseases, including bilateral urinary tract obstruction,[110] autosomal dominant polycystic kidney disease and medullary cystic kidney disease,[111] renal amyloidosis[112] and Sjögren's syndrome.[113] In the last two conditions, amyloid deposits and lymphocytic infiltration around the collecting tubules are responsible for the decline in AVP responsiveness. A decline in urinary concentrating ability is also common in patients with acute or chronic kidney disease. The decrease in the number of functioning nephrons in patients with acute or chronic kidney disease forces the remaining nephrons to excrete a larger proportion of the total solute load. Despite the impairment in concentrating ability, patients with acute or chronic kidney disease do not usually develop polyuria because the glomerular filtration rate is substantially reduced, and urine osmolality is usually isosmotic or only slightly hypoosmotic to plasma.[114]

Drug-induced NDI

Symptoms as a result of lithium toxicity are observed as early as 8 weeks after treatment with lithium carbonate. Lithium is filtered and reabsorbed by the kidney similar sodium, and thus enters into the collecting duct cells.[10,115] Accumulation of cytotoxic concentrations of lithium ultimately leads to a decrease in *AQP2* expression. The coexistence of hypercalcaemia may potentially increase further the risk of NDI. Other drugs such as penicillins, tetracyclines, aminoglycosides and anti-fungals can also induce NDI (Table 3).[33,116–119] Cidofovir[96] and foscarnet,[120] as well as other anti-retroviral drugs and AVPR2 antagonists such as tolvaptan, can also induce a transient state of NDI.[121–123] In the distal nephron, somatostatin analogues may also inhibit AVP action and increase basal water permeability, leading to increased diuresis and NDI, although this appears to be uncommon.[124]

Bartter syndrome

There are several congenital polyuric-polydipsic Bartter-like syndromes associated with urinary concentrating defects of varying

severity.[107] Bartter-like syndromes belong to inherited hypokalaemic salt-losing tubulopathies as a result of mutations in the *Melanoma associated antigen D2* gene (*MAGED2*).[125] Patients with cNDI experience polyuria but have normal conservation of sodium, potassium, chloride and urinary calcium. Patients bearing inactivating mutations in one of the five following genes associated with Bartter syndrome (*SLC12A1*, *KCNJ1*, *CLCNKB*, *CLCNKA* and *CLCNKB* in combination, or *BSND* encoding the membrane proteins of the thick ascending limb of the loop of Henle) have a complex polyuric-polydipsic syndrome with loss of water, sodium, chloride, calcium, magnesium and potassium.

4 | DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diabetes insipidus needs to be differentiated from the more common complaints of frequency or nocturia, which are not associated with an increase in total urine output.[4,126] The differential diagnosis includes a variety of conditions such as osmotic and water diuresis.[127] The amount of urine output varies in CDI depending on the deficient secretion of AVP. In its complete form, the urinary concentrating capacity is severely impaired with urinary osmolality less than 300 mOsm kg^{-1}, whereas in the partial form urine osmolality ranges between 300 and 800 mOsm kg^{-1}. Complete cNDI is typically associated with urine output, as high as 12 L daily, compared to the acquired forms of NDI where polyuria is usually of moderate severity (3–4 L day^{-1}).

PP is characterised by an abnormal thirst perception, which may lead to increase water intake and consequent a polyuria state resembling DI, also called dipsogenic DI. This condition is not a distinct form of DI per se because it is not associated with abnormalities in AVP synthesis or action. PP is characterised by an appropriate excretion of dilute urine, in contrast to CDI and/or NDI that exhibit inappropriate increased output of relatively dilute urine. Because of excess fluid intake, serum osmolality is reduced and AVP secretion is suppressed. PP can also be induced by hypothalamic lesions that directly affect the thirst centres in sarcoidosis[128] or tuberculous meningitis, in hypothalamic tumours, brain injury, hippocampal deformations or lesions in the amygdala.[129–131]

Another polyuric state that needs to be differentiated from DI is solute (osmotic) diuresis. This is a result of the presence of a solute or osmotic diuresis and an inability to reabsorb a substantial proportion of the filtered solute. Solute diuresis is associated with increased volume of urine output with relatively high osmolality. The most important or common solutes include glucose, urea, sodium and mannitol. Sodium-glucose co-transporter 2 inhibitors also diminish renal glucose absorption producing glycosuria and osmotic diuresis.[132] Urea diuresis is another form of solute diuresis that most often occurs in patients with resolving acute kidney injury. Sodium diuresis is usually caused by the administration of large volumes of i.v. saline or after relief of bilateral urinary tract obstruction. Mannitol, usually given to treat increased intracranial pressure, can also induce an osmotic diuresis and polyuria. All of these diagnoses should be readily apparent clinically.

4.1 | Biochemical investigations of DI

In patients with suspected polyuria, 24-h urine volume should initially be assessed to confirm the presence of polyuria. Urine osmolality, sodium, potassium, calcium, creatinine, urea nitrogen and glucose levels should be measured in a 24-h sample, along with additional serum measurements.

4.1.1 | Serum sodium concentration and urine osmolality

A high serum sodium concentration (≥ 147 mmol L^{-1}) and/or serum osmolality (> 300 mOsm kg^{-1}) point towards either osmotic diuresis or, if the urine osmolality is less than the serum osmolality, possible DI. A low serum sodium concentration (< 135 mmol L^{-1}) with a low urine osmolality (< 300 mOsm kg^{-1}) is highly suspicious of PP.[128] Patients with polyuria and a urine osmolality (< 300 mOsmol kg^{-1}) may have either DI or PP. A normal serum sodium concentration in association with a urine osmolality > 600 mOsmol kg^{-1} virtually excludes DI and directs to the diagnosis of solute-osmotic diuresis. To determine whether a solute diuresis is present, the total daily osmolar output can be calculated as the urine osmolality × the 24-h urine volume. If the total daily osmolar output is > 1000 mOsmol, then solute diuresis is most likely present.

4.1.2 | Dynamic tests and copeptin measurement

The diagnosis may be obvious based on simple serum and urinary osmolalities. If the serum osmolality is greatly increased with concomitant low urinary osmolality, especially when there is a known HP-lesion, no further testing may be necessary. When there is a suggestion of polyuria and polydipsia clinically, and serum osmolality is not greatly disturbed, some form of dynamic testing is required.

Classically, water deprivation tests have been performed.[133,134] However, direct measurement of plasma AVP is seldomly performed because AVP is a small peptide with rapid clearance. More recently, assessment of copeptin levels, either with hypertonic saline infusion or more conveniently with L-arginine or glucagon stimulation, was shown to be the most convenient and accurate way of assessing the presence of DI.[135]

Copeptin (C-terminal peptide of pro-vasopressin) is co-secreted with AVP and is more stable.[136,137] Initial data suggested that baseline copeptin levels < 2.6 pmol L^{-1} exhibited a 95% sensitivity and 100% specificity with respect to diagnosing complete CDI and distinguishing CDI from PP. Unfortunately, the complete distinction between CDI and in particular partial CDI and PP is not always definite because of the considerable overlap in baseline copeptin levels.[138] To improve the diagnostic accuracy of the test, measurement of copeptin levels has been suggested after performing hypertonic saline[133] or arginine stimulation,[139] as described below. By contrast to the ambiguous role of baseline levels of copeptin for distinguishing central DI from PI,

copeptin baseline levels > 21.4 pmol L^{-1} are indicative of NDI with 100% sensitivity and specificity.[4,140,141]

Following hypertonic saline administration copeptin level of < 4.9 pmol L^{-1}, in the presence of a serum sodium level > 147 mmol L^{-1}, suggests CDI, whereas higher levels are indicative of PP with a diagnostic accuracy of 95.6%, with 93% sensitivity and 100% specificity.[133] Arginine is an endogenous precursor to nitric oxide, an important signalling molecule in several endocrine pathways, also used for stimulating growth hormone secretion. A copeptin level > 3.8 pmol L^{-1} taken 60 min after arginine infusion indicates PP with a high diagnostic accuracy of 93% (92% sensitivity, 93% specificity).[139] A particular advantage of the arginine infusion test is that it is safe and well-tolerated, with only mild adverse effects, mainly nausea. Nevertheless, if the suspicion for CDI remains high in addition to an arginine-stimulated plasma copeptin > 3.8 pmol L^{-1}, then the response of copeptin to the administration of 3% hypertonic saline followed by desmopressin can be utilised[141]: 250 mL of 3% hypertonic saline saline is given as a bolus followed by a body weight-adapted infusion rate aiming at a serum sodium level ≥ 150 mmol L^{-1} (Figure 4).

A randomised multicentre prospective study is currently being carried out (clinical trials.gov NCT03572166) aiming to confirm the arginine-stimulated copeptin cut-off levels.

5 | IMAGING

In patients with CDI, pituitary MRI can help narrow down the differential diagnoses. Besides the presence of a distinct pathology in the region,[4] the absence of the so-called "bright spot", an area of hyperintensity in the posterior pituitary gland that represents stored AVP or oxytocin in neurosecretory granules, is suggestive but not diagnostic of CDI[142,143] (Figure 5). Although the absence of the bright spot was found in 70% of patients with CDI,[133] it was also absent in 39% of patients diagnosed with PP.[133]

Cranial MRI may also help determine the specific cause of CDI.[144,145] A further characteristic finding suggestive of CDI in the absence of other pathologies is the presence of thickening of the pituitary stalk. Pituitary stalk thickening is considered when the maximum transverse dimension of the pituitary stalk is above 3.25 mm at the level of the optic chiasm, or above 1.91 mm at the insertion of the neurohypophysis.[21] The likelihood that pituitary stalk thickening is associated with autoimmune CDI is 25%, increasing to 80%–82% when CDI is diagnosed in individuals less than 30 years of age and in the presence of other autoimmune diseases.[93]

Stalk thickening of 4 mm or more at the optic chiasm, 3 mm or more at pituitary insertion, or both, is potentially pathological.[16,146] Although pituitary stalk thickening points towards the presence of inflammatory or infiltrative diseases, it is not specific for CDI.[133] Furthermore, in children, progressive thickening of the stalk is strongly suggestive of a germinoma. In a recent meta-analysis including 1368 patients presenting with CDI and thickening of the pituitary stalk, the most common pathologies were germ cell tumours (14.0% of the study population), LCH (10.2%) and metastatic disease (4.7%).[144]

^{18}Fluoro-deoxyglucose-positron emission tomography (i.e., ^{18}FDG-PET) may be utilised when the cause is unclear, especially when the initial differential diagnosis includes other pathologies.[147,148] When an initial MRI does not establish the probable cause of CDI, serial MRI imaging is recommended before a diagnosis of "idiopathic CDI" can be made.[8] Some studies have recommended imaging every 3–6 months for up to 3 years. There are no specific imaging findings that can be employed in patients with NCI.[8]

6 | TREATMENT

6.1 | CDI

The "gold-standard" treatment of CDI is vasopressin/AVP replacement. Currently, desmopressin, a synthetic analogue of vasopressin specific for the V2 receptor, is widely utilised. This compound displays a longer half-life following the removal of the cysteine amino group from native AVP, thus being relatively resistant to vasopressinase activity, and exerts no vasopressor effects following the substitution of L-arginine with D-arginine.[71–73,140]

Desmopressin can be given intranasally or sublingually (buccal preparation), orally (tablet or disintegrating tablet) and in parenteral formulations.[140] The intranasal form is usually given at dose 5–10 μg, whereas the oral formulation is 100–200 μg, with a maximum dose of 1000 μg daily. When parenteral administration is required, it is initiated at doses of 1 μg s.c. or i.m., although smaller doses might be used.

The most important adverse events associated with desmopressin therapy are mild hyponatraemia developing in approximately 27% of CDI patients and severe hyponatraemia in 15% according to one report.[149] One of the largest surveys of patients with CDI showed that patients who routinely omitted or delayed desmopressin had a significantly lower prevalence of hyponatraemia compared to those not utilising this approach (odds ratio = 0·55; 95% confidence interval = 0.39–0.77; p = .0006).[150] Electrolyte monitoring is recommended 1–2 days after treatment initiation, and should be repeated until a stable dose of desmopressin is achieved.[4,151]

Data regarding oxytocin deficiency in patients with panhypopituitarism or CDI are scarce. Thus, the need for replacement treatment remains mainly theoretical, although a cross-sectional study demonstrated that low oxytocin levels were associated with lower bone mass density and less favourable hip geometry,[152] as well as with cognitive impairment. Preliminary results provide some evidence of potential benefits of oxytocin therapy with respect to improving these deficits and accompanying metabolic disturbances.[153,154] Oxytocin is currently administered as an i.v. preparation to induce or augment labour and for the treatment of post-partum haemorrhage. Neither of these modes of delivery are viable as a long-term treatment option because of the very short half-life of oxytocin. Longer-acting oxytocin analogues such as carbetocin, [Ser4, Ile8]-oxytocin and [Asu1,6]-oxytocin have been shown to reduce weight and improve glucose

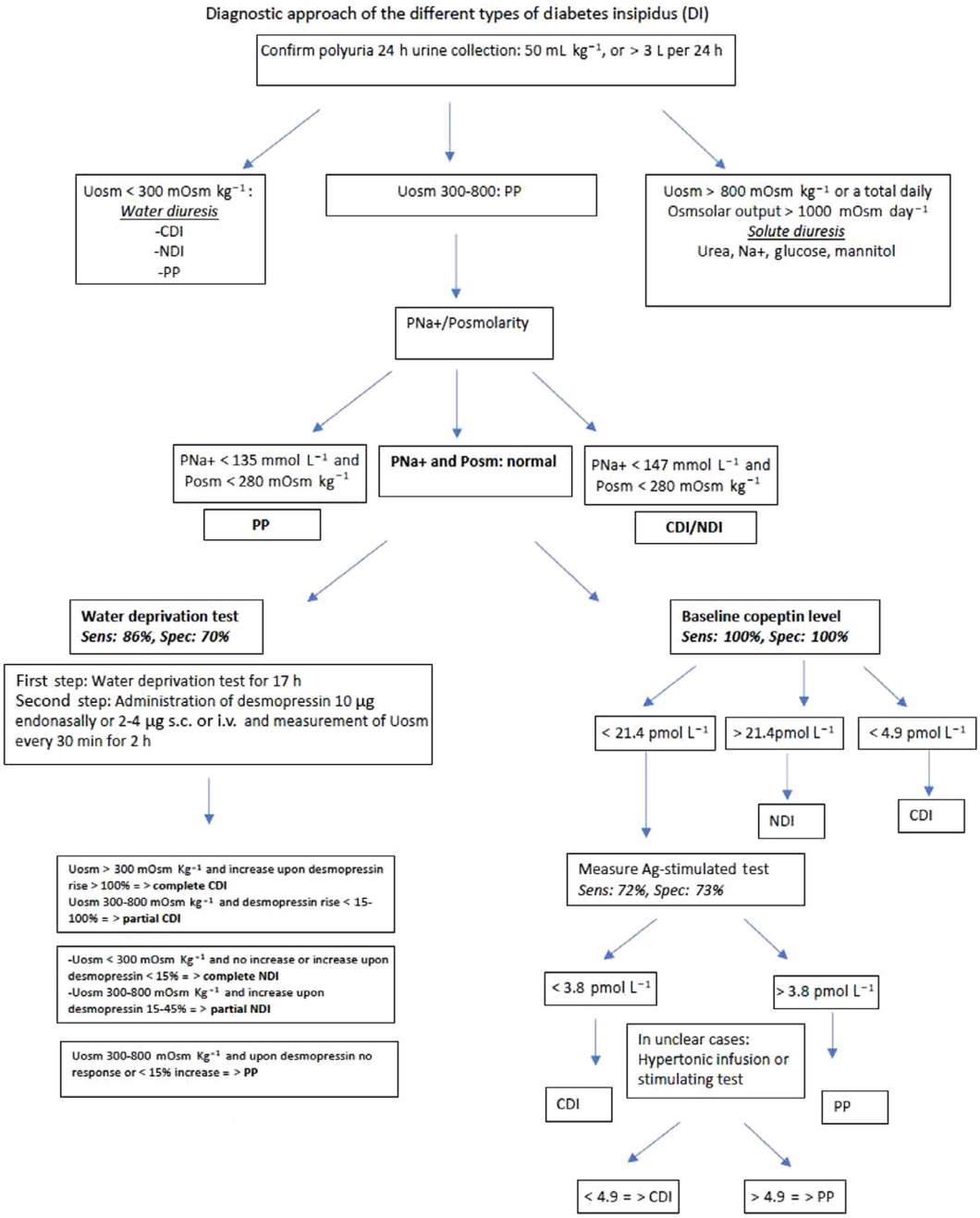

FIGURE 4 An algorithm for the diagnostic approach of the different types of diabetes insipidus (DI). Abbreviations: P, plasma; U, urinary; osm, osmolality; CDI, central diabetes insipidus; NDI, nephrogenic diabetes insipidus; PP, primary polydipsia; sens, sensitivity; spec, specificity

regulation in obese diabetic mice. However, human data are currently lacking.

6.1.1 | Post-operative CDI

Transient or permanent CDI may be caused following sellar/parasellar surgery.[88] In cases of mild DI in the presence of an intact thirst mechanism, adequate access to water may compensate for the fluid loss if the patient is capable of drinking. In general, desmopressin is prescribed if polyuria persists beyond 48 h.[140] After desmopressin administration, monitoring is suggested every 3 h.[88,155] In some cases, partial DI may be masked in the presence glucocorticoid deficiency because water cannot be effectively excreted in this situation and the CDI becomes apparent only after glucocorticoid replacement.[7,156] A single dose of subcutaneous or i.v. desmopressin, usually 1–2 µg as a first dose, may be sufficient to resolve a transient and/or partial CDI, but when urine output increases again > 250 mL h^{-1} for 2 h associated with low urine specific gravity and/or osmolality, a further dose may be

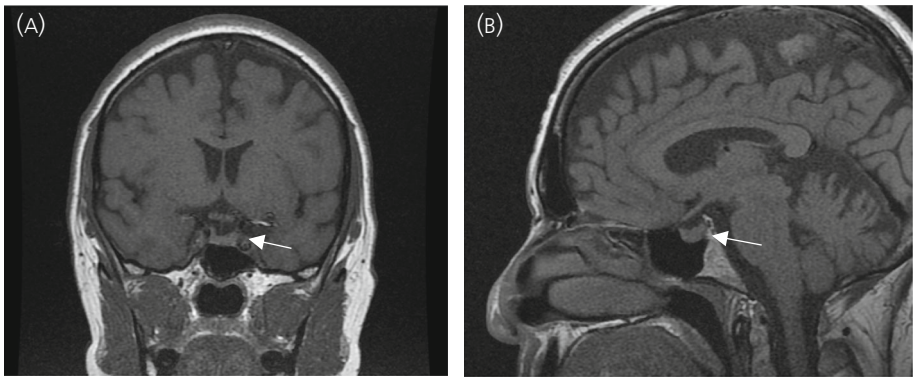

FIGURE 5 Magnetic resonance imaging of a young patient with idiopathic diabetes insipidus showing the absence of the bright spot of the posterior pituitary gland (white arrow). (A) Non-contrast T1 coronal sequence. (B) Non-contrast T1 sagittal sequence

administered along with continuous monitoring to avoid water intoxication and hyponatraemia.[15]

6.1.2 | Adipsic CDI

In cases of adipsic CDI, regular water intake and standard doses of desmopressin are administered along with regular daily weighting, aiming at maintain a meticulous fluid balance without alterations of body weight. Regular monitoring of serum sodium and osmolality is necessary when the patient is admitted into hospital.[156]

6.1.3 | ICI-induced CDI

CDI has been described after several days of ICI treatment: desmopressin combined with glucocorticoid may be needed to treat both DI and ACTH deficiency.[6,82] Currently, several relevant guidelines have been published addressing the decision to administer or discontinue the triggering ICI(s) based on clinical judgment of the performance status of the patient, and the type of underlying malignancy.[157–159] Recent guidelines suggest that a controlled endocrinopathy is not a contraindication for initiation and/or continuation of ICI therapy; furthermore, most endocrine dysfunction appears to be permanent regardless of ICI discontinuation. Thus, the development of endocrinopathies does not dictate a need to stop ICI treatment.[159]

6.2 | NDI

Management of NDI includes the discontinuation of any causative medications and/or reversing any underlying condition. After fluid replacement and reduction of the solute load, thiazide diuretics and non-steroidal anti-inflammatory drugs (e.g., indomethacin) can be administered. Thiazide treatment can reduce, urine output by almost 70% when given in combination with a low-solute diet.[5] The addition of amiloride, a potassium-sparing diuretic, further reduces urine volume. Carbamazepine acts also on the renal collecting ducts by increasing the expression of AQP-2 channels, and can be also used in NDI. In the majority of patients with non-hereditary NDI, resistance to AVP is only partial, and patients may be responsive to desmopressin, although higher doses may be required.[2,4,7,44]

Lithium-induced NDI is a major clinical problem. A recent systematic review recommended the use of a once-daily dosing schedule, with the minimum serum lithium level that is effective to prevent lithium intoxication.[46] Chlorothiazide has also been given, combined with a sodium-deplete diet (4 g day^{-1}), resulting in a significant reduction of urine volume and an increase in maximal urine osmolality.[47] Acetazolamide has been also given in a patient with lithium-induced NDI, inducing an increase of urine osmolality from 250 to 339 mOsmol kg^{-1} H_2O.[48]

6.2.1 | DI and COVID-19

With COVID-19 infection, special recommendations suggest the use of oral instead of nasal desmopressin, and patients are advised to drink more water.[5] However, when cognitive function becomes distorted by fever, hypoxia or sepsis, i.v. fluids may be required along with i.v. desmopressin at a starting dose of 0.5 μg s.c.[6] During COVID-19 infection, patients with established DI may need diuretic therapy in the presence of lung or the kidney involvement leading to dehydration and hypernatraemia.[45] In cases of acute respiratory distress syndrome with pulmonary oedema and/or acute kidney injury, hypernatraemia should not be overcorrected, aiming only for a serum sodium level of < 155 mmol L^{-1} considering the risk of venous thrombosis and pulmonary embolism.[51] When severe dehydration is not accompanied by hypovolaemic shock, patients with DI should receive hypotonic fluids, orally with water and i.v. with 5% dextrose. The replacement rate of water aims to exceed the hourly urine output and reverse the calculated total body water deficit to slowly normalise serum sodium (target-rate of < 0.5 mmol L^{-1} h^{-1}) (< 10–12 mmol L^{-1} day^{-1}).[49]

6.3 | Gestational DI

Desmopressin is the treatment of choice in all types of GDI despite the absence of any clinical trials.[160] Desmopressin is resistant to placental vasopressinase, and displays little oxytocic activity, and is

unlikely to induce uterine contractions.[13] In case of preexisting CDI on desmopressin replacement therapy, treatment can be continued during pregnancy, usually necessitating an increase in the administered dose. A higher dose is needed during the progression of pregnancy, with the highest doses given in late pregnancy because of a further increase of placental vasopressinase levels degrading any residual AVP.[10] Desmopressin following labour can be discontinued or given at lower doses; it appears to be safe for the mother and fetus, with only oligohydramnios being reported as a rare complication.[50,161,162] Desmopressin can also be given during lactation because it does not enter into the breast milk.[160,163] NDI management is more difficult during pregnancy because diuretics and non-steroidal anti-inflammatory drugs are generally contra-indicated, whereas the low-protein, low-salt diet effect has not been studied.[110] In the case of severe hypernatraemia, pregnant women should to be admitted to a critical care facility to correct sodium levels slowly by i.v. administration of hypotonic fluids at a rate of 1 mmol L^{-1} h^{-1}, targeting to a rate adjusted to exceed the hourly urine output, providing sufficient water to normalise serum sodium at a rate of < 0.5 mmol L^{-1} h^{-1} (< 10–12 mmol L^{-1} day^{-1}).[4,10,155]

6.4 | Newly evolving therapeutic agents

Advances in molecular diagnosis have opened the horizon for emerging experimental drugs that may either replace the action of basolateral surface or tubular lumen receptors, or by-pass the need when there is receptor malfunction.[7] Molecular chaperones, a family of proteins playing a vital role in the stabilisation of unfolded proteins, have been used to rescue mutant V2 receptors and induce proper intracellular folding and cell surface trafficking.[7] A pilot study in five adult men with NDI (V2 receptor defect) demonstrated a reduction in urine volume from 12 to 6 L day^{-1}, and in water intake from 11 to 7 L day^{-1}, using a non-peptide V1a receptor "antagonist" (SR49059).[164]

An alternative mechanism is to increase cAMP activity or availability because cAMP is considered a major activator of AQP2.[165] A number of agents are already in use for other indications, and ligands of G protein-coupled receptor have been investigated as potential drugs for NDI therapy. Secretin with or without fluvastatin, simvastatin and aminoglycosides has been investigated in preclinical and clinical studies, although none of these to date has been able to demonstrate clinically meaningful results.[166–168] Atorvastatin was investigated in a double-blind, randomised, placebo-controlled trial in patients on lithium therapy, but, when used at a dose of 20 mg day^{-1}, did not improve urinary osmolality compared to placebo over a 12-week period.[168] Clopidogrel, a P2Y12 inhibitor that activates G protein-coupled receptor, or sildenafil, a phosphodiesterase inhibitor, which inhibits cAMP degradation, have also been assessed, with urine osmolality improving in a patient with X-linked NDI treated with sildenafil.[167,169] However, in a clinical trial sildenafil, or riociguat, increased cGMP levels without improving urinary concentration ability in patients with congenital NDI.[170] In addition, metformin, a stimulant of AMP-activated protein kinase, was also studied in a clinical trial of patients with congenital NDI, although it failed to show any significant benefit (ClinicalTrials.gov: NCT02460354).

Targeting miRNA-137[68] and miR-32, as well as tropomyosin-5b (TM5b), which are essential for AQP2 trafficking, may at least theoretically treat NDI.[171] In addition, AKAP-PKA disruptors, such as the low-molecular weight compound 3,30-diamino-4,40-dihydroxydiphenylmethane (i.e., FMP-API-1) and its derivatives, increase AQP2 activity to the same extent as vasopressin.[172] Thus, AKAP-PKA disruptors also constitute a novel category of potential therapeutic drugs for NDI, and are the first low-molecular weight compounds that can phosphorylate AQP2 more effectively than pre-existing drug candidates.[172]

7 | CONCLUSIONS AND FUTURE DEVELOPMENTS

Diabetes insipidus is characterised by the decreased synthesis, release or action of AVP, which may be partial or complete. Acquired CDI or "AVP-deficiency" as a result of trauma or surgery is the most common form of DI. New causes of CDI have recently emerged following the wide use of immunotherapy in patients with cancer along with cases related to COVID-19 infection. Rare causes of familial CDI as a result of specific genetic defects have also been described. The diagnosis is based on the presence of polyuria, low urine osmolarity along with high serum sodium and osmolality, but is substantiated further with copeptin measurement following either hypertonic saline infusion or more simply with arginine stimulation.

Treatment of established CDI is based on the administration of desmopressin, when adipsic DI cases necessitates meticulous water and desmopressin administration along with active patient participation or that of their carer. NDI or "AVP-resistance" is less common than CDI and is a result of resistance to AVP action secondary to diseases affecting the kidney or nephrotoxic drugs. A number of genetic abnormalities involving the AVP receptors and proteins involved in water transfer are increasingly recognised.

Treatment of NDI is more complex, requiring the use of a low solute diet and medications such as diuretics and, in some cases, higher doses of desmopressin. Further work is needed to identify additional genetic, epigenetic or modifying factors that may further elucidate the pathogenesis of specific forms of DI and lead to a more personalised treatment based on the specific aetiology.

AUTHOR CONTRIBUTIONS

Anna Angelousi: Data curation; methodology; resources; writing – original draft. **Krystallenia Alexandraki:** Data curation; methodology; writing – original draft. **Chrysoula Mytareli:** Data curation; resources. **Ashley B Grossman:** Conceptualization; supervision; validation; writing – review and editing. **Gregory Kaltsas:** Conceptualization; supervision; writing – review and editing.

ACKNOWLEDGEMENTS

Chrysoula Mytareli was supported by a grant from the Foundation for Education and European Culture.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/jne.13233.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this review because no new data were created or analysed.

ORCID

Anna Angelousi https://orcid.org/0000-0003-0906-3617
Krystallenia I. Alexandraki https://orcid.org/0000-0003-2398-6768
Ashley B. Grossman https://orcid.org/0000-0003-1176-6186

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How to cite this article: Angelousi A, Alexandraki KI, Mytareli C, Grossman AB, Kaltsas G. New developments and concepts in the diagnosis and management of diabetes insipidus (AVP-deficiency and resistance). *J Neuroendocrinol*. 2023;35(1):e13233. doi:10.1111/jne.13233