Diabetes insipidus

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Abstract | Diabetes insipidus (DI) is a disorder characterized by excretion of large amounts of hypotonic urine. Central DI results from a deficiency of the hormone arginine vasopressin (AVP) in the pituitary gland or the hypothalamus, whereas nephrogenic DI results from resistance to AVP in the kidneys. Central and nephrogenic DI are usually acquired, but genetic causes must be evaluated, especially if symptoms occur in early childhood. Central or nephrogenic DI must be differentiated from primary polydipsia, which involves excessive intake of large amounts of water despite normal AVP secretion and action. Primary polydipsia is most common in psychiatric patients and health enthusiasts but the polydipsia in a small subgroup of patients seems to be due to an abnormally low thirst threshold, a condition termed dipsogenic DI. Distinguishing between the different types of DI can be challenging and is done either by a water deprivation test or by hypertonic saline stimulation together with copeptin (or AVP) measurement. Furthermore, a detailed medical history, physical examination and imaging studies are needed to ensure an accurate DI diagnosis. Treatment of DI or primary polydipsia depends on the underlying aetiology and differs in central DI, nephrogenic DI and primary polydipsia.

Diabetes insipidus (DI) is a form of polyuria–polydipsia syndrome and is characterized by hypotonic polyuria (excessive urination; >50 ml/kg body weight/24 h) and polydipsia (excessive drinking; >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 (of central or renal origin) and secondary forms (resulting from primary polydipsia) of polyuria. A third, rare form of DI termed gestational DI can occur during pregnancy. Central DI (also known as hypothalamic or neurogenic DI) results from inadequate secretion and usually deficient synthesis of arginine vasopressin (AVP) in the hypothalamic–neurohypophyseal system in response to osmotic stimulation (FIG. 1). Central DI is most often an acquired disorder that is caused by disruption of the neurohypophysis (specifically, damage to the AVP-producing magnocellular neurons), whereas hereditary forms are less common and are caused by mutations in *AVP*[2] (located on the short arm of chromosome 20 (20p13)). Nephrogenic DI is the result of an inadequate response of the kidneys to AVP, either due to mutations in AVP receptor 2 (*AVPR2*) or aquaporin 2 (*AQP2*)[3] (hereditary nephrogenic DI) or as an adverse effect of various drugs, most commonly lithium, or due to electrolyte disorders, such as hypercalcaemia or hypokalaemia (acquired nephrogenic DI). Primary polydipsia is characterized by excessive fluid intake that leads to polyuria, despite intact AVP secretion and an appropriate antidiuretic renal response. Gestational DI results from the enzymatic breakdown of endogenous AVP by increased placental vasopressinase levels in pregnancy.

Regardless of the aetiology, all four forms of polyuria–polydipsia syndrome result in a water diuresis due to an inability to maximally concentrate urine. Distinguishing between the types of DI is important, as treatment strategies differ and application of the wrong treatment can be dangerous[4]. However, DI is often difficult to diagnose reliably and accurately[5], especially in patients with primary polydipsia or partial, mild forms of central and nephrogenic DI[1,6]. In this Primer, we describe the different types of DI, their pathophysiology, the methods for differentiating between them and therapies for optimal management of each type of DI. We also discuss possibilities for prevention and available data about quality of life (QOL) in patients with DI.

Epidemiology

Prevalence

DI is a rare disease with a prevalence of ~1 in 25,000 individuals[7] and data on geographical differences in prevalence are limited. The disorder can manifest at any age, and the prevalence is similar among males and females. The age at presentation depends markedly on the aetiology[8,9], with hereditary forms manifesting early in life, whereas acquired forms manifest after early childhood. Although precise prevalence data are not available, acquired forms of DI are much more common than familial forms. Fewer than 10% of cases of renal and central DI are hereditary. In a study involving 79 paediatric patients,

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DI was found to be familial in only 6% of the patients and the remaining 94% had various types of acquired DI[9].

Central DI is the most common type of DI. In hereditary central DI, the predominant inheritance pattern is autosomal dominant due to mutations in *AVP*, although rarely it can be due to the autosomal recessive disorder Wolfram syndrome, which is caused by mutations in *WFS1* (encoding wolframin). Only few population-based data on the incidence of congenital nephrogenic DI exist, but estimates can be made. X-linked nephrogenic DI due to loss-of-function mutations in *AVPR2* accounts for ~90% of hereditary nephrogenic DI cases and was reported to occur with a frequency of ~8.8 cases per million male live births in the general population of Quebec[10], which might be representative of the general population worldwide[3]. Autosomal recessive and autosomal dominant nephrogenic DI due to loss-of-function mutations in *AQP2* accounts for the remaining ~10% of hereditary nephrogenic DI cases[3,7]. The prevalence of acquired nephrogenic DI in patients receiving long-term lithium treatment is 30%.

Primary polydipsia is common in patients with neurodevelopmental disorders (such as autism and intellectual disability) or psychotic disorders (such as schizophrenia, schizoaffective disorder, bipolar disorder and psychotic depression), particularly chronic schizophrenia, in which primary polydipsia occurs in 11–20% of patients[11]. Many of these patients experience episodes of hyponatraemia, especially during psychotic relapses, a syndrome often referred to as psychosis intermittent hyponatraemia–polydipsia (PIP) syndrome[12]. Many other individuals with non-psychotic Axis I psychiatric disorders also have primary polydipsia, a form that is often termed compulsive water drinking (CWD; also known as psychogenic polydipsia)[11]. These patients rarely if ever become hyponatraemic in the absence of other factors (such as treatment with thiazide diuretics). Outside the psychiatric setting, the prevalence of CWD is increasing in the general population (and seems to be more prevalent in women) owing to the increasing popularity of lifestyle programmes and the current view that fluid intake is inadequate and that drinking water is healthy and improves cognition in children and adults[13,14]. The extent to which these patients overlap with those with dipsogenic DI (that is, DI owing to an abnormally low thirst threshold) is unknown.

DI during pregnancy was first reported in 1942 and occurs in ~1 in 30,000 pregnancies, with the highest prevalence in multiparous women. Gestational DI typically occurs at the end of the second or early third trimester (the peak of placental vasopressinase production) and is associated with a higher risk of pre-eclampsia[15]. Pre-existing asymptomatic partial central DI can become symptomatic during pregnancy, owing to the inability of the pituitary gland to increase AVP secretion in response to increased degradation of AVP by placental vasopressinase[16]. In these patients, symptoms typically appear early in pregnancy and recur with every pregnancy. The severity of polyuria and polydipsia in patients with pre-existing central DI may increase in pregnancy.

Risk factors

Central DI. Risk factors for central DI include traumatic and non-traumatic causes of damage to AVP-producing magnocellular neurons in the hypothalamus. The most common risk factor for trauma-induced central DI is surgical resection of tumours in the sellar and suprasellar area. Although tumours contained within the sella turcica, such as pituitary macroadenoma, rarely cause DI, surgical resection of these tumours and subsequent damage to the axons of the AVP-producing magnocellular neurons in the pituitary stalk (also known as the infundibulum) can result in central DI. The incidence of postoperative DI is substantially higher following resection of large suprasellar tumours, such as craniopharyngioma (10–25% incidence, depending on the extent of resection[17]), compared with resection of sellar-based tumours, such as pituitary microadenoma or macroadenoma (5–30% incidence of transient DI but only 1–4% incidence of permanent DI[18,19]). Resection of tumours with a more rostral location has a greater risk of causing adipsic central DI because of damage to osmoreceptors in the anterior hypothalamus (FIG. 2). Traumatic brain injury can also lead to central DI — in particular, deceleration injuries that shear the pituitary stalk at the level of the diaphragma sellae, leading to a characteristic triphasic response (TABLE 1).

Risk factors for non-traumatic central DI include genetic mutations (TABLE 1), granulomatous diseases that infiltrate the hypothalamus (such as sarcoidosis and Langerhans and non-Langerhans cell histiocytosis), primary brain tumours that invade or compress the hypothalamus (such as germinoma, meningioma, craniopharyngioma and lymphoma), secondary tumours in the pituitary gland or pituitary stalk (usually metastatic breast or lung tumours) and lymphocytic infundibuloneurohypophysitis (LIN) that causes autoimmune destruction of AVP neurons[20]. Although the occurrence of LIN is usually unpredictable, some risk factors have been identified, including states associated with activation of autoimmune diseases, such as the post-partum period, personal or family history of autoimmune disorders, anterior pituitary hypophysitis, chronic inflammation of parasellar structures (for example, in hypertrophic pachymeningitis and Tolosa–Hunt syndrome), IgG4-related systemic diseases (such

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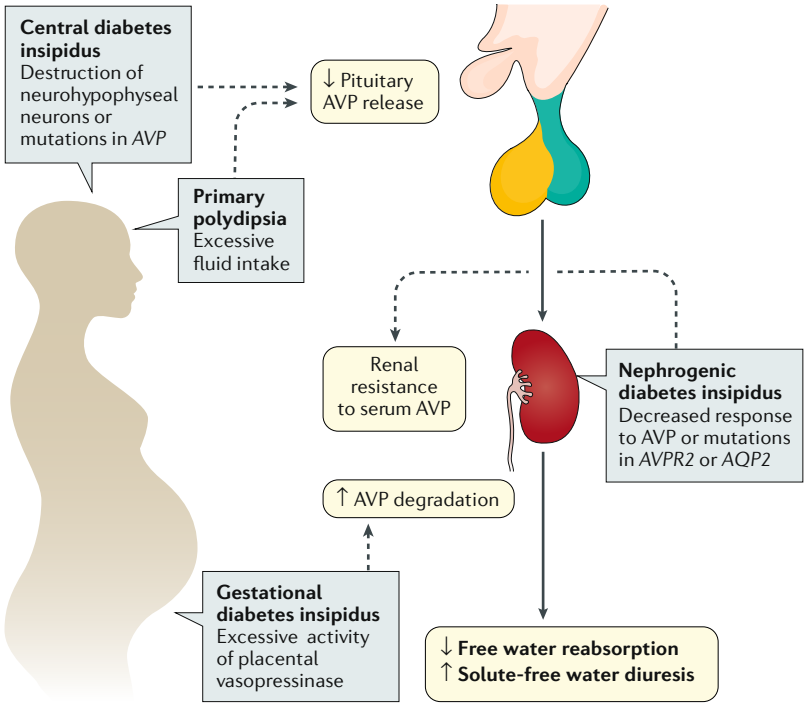

Fig. 1 | **Pathophysiology of DI.** Diabetes insipidus (DI) is a form of polyuria–polydipsia syndrome, which is caused by various acquired or hereditary lesions or disorders. Central DI results from inadequate production and/or secretion of arginine vasopressin (AVP) in the hypothalamic–neurohypophyseal system in response to osmotic stimulation. Acquired central DI is caused by disruption of the neurohypophysis, whereas hereditary central DI is due to mutations in *AVP*. Nephrogenic DI is the result of an inadequate response of the kidneys to AVP, either acquired (as an adverse effect of various drugs or due to electrolyte disorders) or hereditary (due to mutations in the genes encoding arginine vasopressin receptor 2 (AVPR2) or the water channel aquaporin 2 (AQP2)). In primary polydipsia, excessive fluid intake that leads to polyuria occurs, even when AVP secretion and an appropriate antidiuretic renal response are present. In gestational DI, increased activity of arginine vasopressinase during pregnancy reduces the levels of AVP, leading to a presentation similar to that of central DI.

as autoimmune pancreatitis and lymphoproliferation)[21] and the presence of anti-rabphilin 3A antibodies[22,23].

Nephrogenic DI. Apart from genetic risk factors, the most common risk factors for nephrogenic DI are lithium treatment, hypercalcaemia and hypokalaemia. Lithium is one of the most common medications for treating and preventing relapses of bipolar disorders and psychotic depression. In a study of 873 patients with bipolar disorders who were treated with lithium, of the 54% of patients who discontinued lithium treatment, 9% did so because of polyuria, polydipsia or DI, usually within 5 years. Discontinuation of lithium treatment because of increasing serum creatinine levels (indicative of renal dysfunction) occurred after 17 years on average, although this occurred after 30 years in four patients[24].

Primary polydipsia. Patients with primary polydipsia who have psychotic disorders rarely complain of thirst but instead provide delusional explanations for their excessive drinking or state that drinking reduces their anxiety or makes them feel better[25,26]. Patients with primary polydipsia who have schizophrenia, and the first-degree relatives of these patients, have a higher incidence of alcoholism and smoking than other individuals with schizophrenia[27,28]. Polydipsic patients with schizophrenia can often be identified in the community setting because they have a cup in their hand at all times, drink from toilets and gather around radiators during cold weather[26]. They rarely drink at night compared with patients with DI and their day-time drinking coincides with other stereotypies (such as smoking, pacing and mannerisms)[29]. Hyponatraemia in patients with PIP must be distinguished from that attributable to psychotropic medications (such as antipsychotic drugs or the anticonvulsant carbamazepine) or medications for the treatment of hypertension (such as thiazides) and diabetes (such as chlorpropamide), which is commonly seen in other polydipsic patients with and without schizophrenia[14,27]. The impaired water excretion induced by antipsychotic drugs can be distinguished from that in patients with PIP because it is stable and more marked[30].

The prevalence of CWD is higher in women than in men[14]. Unlike patients with psychotic disorders, compulsive water drinkers are much more likely to complain of excessive thirst and seem to be prone to psychosomatic disorders[31,32]. Many compulsive water drinkers have depression, anxiety, obsessive–compulsive disorder, anorexia nervosa or alcoholism, and others become habituated to drinking owing to fear of dehydration or the belief that water improves health[33].

Dipsogenic DI is inevitably associated with increased thirst and is assumed to involve systemic rather than psychological factors[34]. The extent of overlap between compulsive water drinkers without psychiatric illness and patients with dipsogenic DI is unclear. Because of the absence of distinguishing features (noted above), dipsogenic DI can rarely if ever be definitively distinguished from other forms of DI without assessing the osmotic threshold for thirst[35]. Primary polydipsia associated with organic brain disorders often occurs in conjunction with polyphagia. Hypothalamic sarcoidosis in particular is more likely to enhance water intake than to impair AVP secretion[32].

Gestational DI. Gestational DI typically occurs at the end of the second or early third trimester (the peak of placental vasopressinase production)[36]. Vasopressinase production is proportional to the size of the placenta and thus the risk of gestational DI is higher for twin and multiple pregnancies. Transient gestational DI has also been reported in patients with pre-eclampsia, HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome and acute fatty liver disease (owing to impaired hepatic degradation of vasopressinase)[37].

Mechanisms/pathophysiology

Excessive renal excretion of large volumes of dilute urine in DI is caused by a decrease in the secretion or action of AVP (except in primary polydipsia), which can be partial or almost complete, depending on the underlying cause.

Central DI

Central DI is most often due to various acquired or hereditary lesions that destroy or damage the neurohypophysis, either by pressure or by infiltration (TABLE 1).

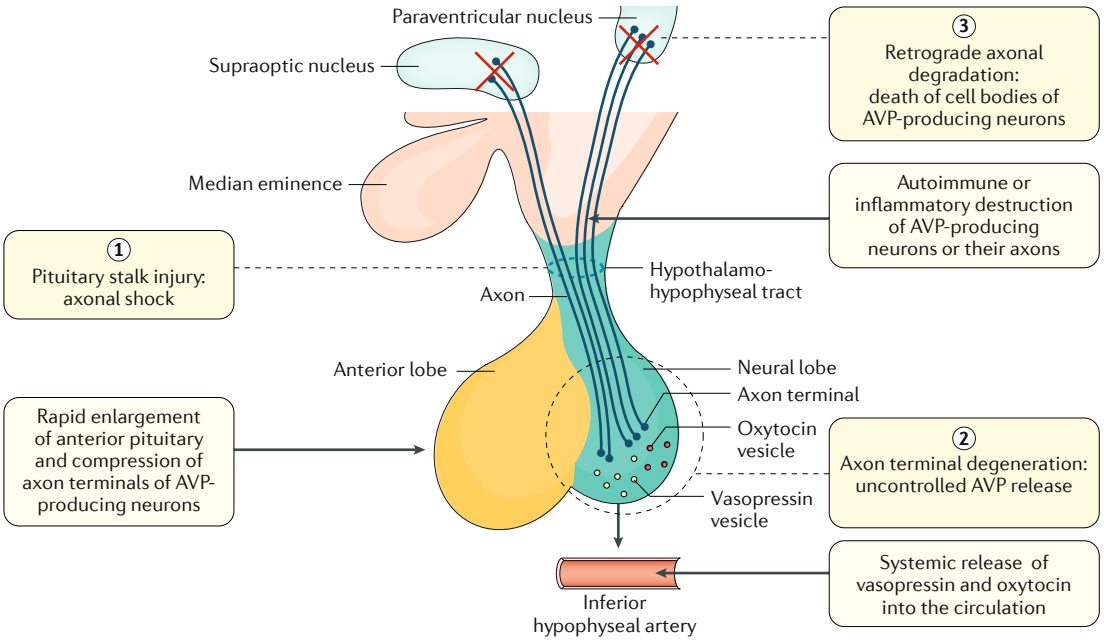

Fig. 2 | **Pathogenetic mechanisms in acquired central DI.** In the triphasic response, the first phase of central diabetes insipidus (DI) occurs after pituitary stalk damage that severs the connections between the cell bodies (in the hypothalamus) and axons (in the posterior pituitary gland) of the arginine vasopressin (AVP)-producing magnocellular neurons, which prevents stimulated secretion of AVP (step 1). This is followed in several days by the second phase, syndrome of inappropriate antidiuretic hormone secretion (SIADH), which is caused by uncontrolled release of AVP from the degenerating nerve terminals in the posterior pituitary gland into the bloodstream (step 2). After all stored AVP in the posterior pituitary gland has been released, the third phase of DI occurs if the cell bodies of >80–90% of the AVP-producing neurons in the hypothalamus undergo retrograde degeneration (step 3). Similar pathogenetic mechanisms underlie autoimmune and inflammatory aetiologies of central DI that result in destruction of axons and cell bodies of AVP-producing neurons, and rapid enlargement of anterior pituitary lesions (for example, metastatic lesions and pituitary apoplexy) that compress the axons of AVP-producing neurons. Adapted with permission from REF.[162], Elsevier.

The severity of the resulting hypotonic diuresis is dependent on the extent of the neurohypophyseal damage, resulting in either partial or complete deficiency of AVP secretion. The levels of oxytocin, the other hormone secreted from the posterior pituitary, also seem to be low in patients with central DI, paralleling an increased psychopathology that is suggestive of a possible oxytocin-deficient state. However, larger studies are required to confirm these findings[38].

Acquired central DI. Despite the large number of lesions that can produce central DI, it is actually more common for patients with these lesions to not develop central DI. This apparent inconsistency is the result of several aspects of neurohypophyseal physiology. First, AVP synthesis occurs in the hypothalamus and not in the posterior pituitary gland, which is only the site of storage and secretion of the AVP-containing neurosecretory granules (FIG. 2). Thus, lesions in the sella turcica that damage only the posterior pituitary gland leave the cell bodies of the AVP-synthesizing magnocellular neurons intact and therefore do not usually cause central DI; for example, the gradual destruction of the posterior pituitary gland by slowly enlarging large pituitary macroadenomas damages only the nerve terminals but not the cell bodies of the AVP-producing neurons, allowing sufficient time for the site of AVP release to shift more superiorly to the pituitary stalk and median eminence. Indeed, the development of DI from a pituitary adenoma is so uncommon that its presence should lead to consideration of alternative diagnoses, such as craniopharyngioma or more rapidly enlarging sellar or suprasellar masses (such as metastatic lesions or acute haemorrhage), which do not allow sufficient time for a shift in the site of AVP release.

Second, the AVP synthesis capacity of the neurohypophyseal neurons considerably exceeds daily needs for maintaining water homeostasis. Destruction of 80–90% of the AVP-synthesizing magnocellular neurons in the hypothalamus following surgical resection of the pituitary stalk is required to produce polyuria and polydipsia in dogs[39]. Thus, even lesions that destroy the cell bodies of these neurons must produce fairly extensive damage to cause DI. Necropsy studies of human patients after pituitary stalk resection showed atrophy of the posterior pituitary gland and loss of the magnocellular neurons in the hypothalamus owing to retrograde degeneration of neurons with axons severed during surgery[40]. Similar to all neurons, the probability of retrograde neuronal degeneration occurring depends on how close the axotomy is to the cell body of the magnocellular neuron. In humans, transection of the pituitary stalk at the level of the diaphragm sellae (that is, a 'low stalk transection') caused only transient central DI, whereas transection at the level of the infundibulum (that is, a 'high stalk transection') caused permanent central DI in most patients[41].

Central DI resulting from surgical or traumatic injury to the neurohypophysis is a unique situation that can result in several different, well-defined phenotypes. In some patients, polyuria develops 1–4 days after the injury but then resolves spontaneously. Less commonly, DI persists for longer periods and may become permanent (this occurs more frequently with suprasellar lesions, such as craniopharyngioma). Most interestingly, pituitary stalk transection can result in a triphasic response. The initial DI (first phase) lasts several hours to several days and is due to axon shock and functional deficiency of the damaged neurons. The second, antidiuretic phase (termed syndrome of inappropriate antidiuretic hormone secretion (SIADH)) can persist for 2–14 days and is due to the uncontrolled release of AVP from the disconnected, degenerating posterior pituitary gland[42]. Importantly, in this second phase, overly aggressive fluid administration does not suppress AVP secretion and can result in hyponatraemia. In the third phase, DI recurs after depletion of the AVP from the degenerating posterior pituitary gland[43].

Idiopathic forms of central DI are a large category; in a study of paediatric patients with central DI, DI was idiopathic in 54% on initial classification[9]. However, longer-term follow up showed a diagnostic accuracy of 96% in those patients initially classified as having idiopathic DI[44]. These patients usually have no history of previous injury or disease that might have contributed to their central DI, and pituitary MRI reveals no abnormalities other than the absence of the posterior pituitary bright spot (PBS; see below) and sometimes thickening of the pituitary stalk. Multiple lines of evidence suggest that autoimmune destruction of the neurohypophysis is the most likely cause of the central DI in many of these patients[20,45], including biopsy samples and post-mortem examination of patients with idiopathic central DI demonstrating lymphocytic infiltration of the pituitary stalk[20,45] and studies demonstrating a high prevalence (67%) of anti-vasopressin cell antibodies in young patients with non-traumatic central DI[46]. Although the presence of anti-vasopressin cell antibodies supports the involvement of an autoimmune process in many cases of idiopathic DI, these antibodies have also been detected in DI of other aetiologies, including Langerhans cell histiocytosis and germinoma, and thus cannot be considered a reliable marker of autoimmune-mediated DI[42]. Furthermore, in a form of infundibulo-neurohypophysitis that occurs in middle-aged to older men and is associated with immunoglobulin G4 (IgG4)-related systemic disease[47], various organs, especially the pancreas, are infiltrated with IgG4-secreting plasma cells, and neurohypophysitis is only one manifestation of a multi-organ disease that may affect other endocrine glands.

Table 1 | **Aetiology of polyuria–polydipsia syndromes**

Basic defect	Acquired causes	Hereditary causes
Central DI		
Deficiency in AVP synthesis or secretion	• Trauma (surgery and deceleration injury) • Neoplasia (craniopharyngioma, meningioma, germinoma and metastases) • Vascular (cerebral or hypothalamic haemorrhage and infarction or ligation of anterior communicating artery aneurysm) • Granulomatous (histiocytosis and sarcoidosis) • Infectious (meningitis, encephalitis and tuberculosis) • Inflammatory or autoimmune (lymphocytic infundibuloneuro-hypophysitis and IgG4 neurohypophysitis) • Drug or toxin exposure • Osmoreceptor dysfunction (adipsic DI) • Others (hydrocephalus, ventricular or suprasellar cyst, and trauma and degenerative diseases) • Idiopathic	• Autosomal dominant: *AVP* mutations • Autosomal recessive, type a and b: *AVP* mutations • Autosomal recessive, type c: *WFS1* mutations • Autosomal recessive, type d: *PCSK1* mutations • X-linked recessive: gene unknown
Nephrogenic DI		
Reduced renal sensitivity to antidiuretic effect of physiological AVP levels	• Drug exposure (lithium, demeclocycline, cisplatin, etc.) • Hypercalcaemia or hypokalaemia • Infiltrating lesions (sarcoidosis, amyloidosis, multiple myeloma, etc.) • Vascular disorders (sickle cell anaemia) • Mechanical (polycystic kidney disease and urethral obstruction)	• X-linked: *AVPR2* mutations • Autosomal recessive or dominant: *AQP2* mutations
Primary polydipsia		
Excessive fluid intake at a diminished set point	• Dipsogenic[a] (idiopathic or similar lesions as with central DI) • Psychosis intermittent hyponatraemia–polydipsia (PIP) syndrome • Compulsive water drinking • Health enthusiasts	NA
Gestational DI		
Increased enzymatic metabolism of circulating AVP hormone	Pregnancy	NA

[a]Downward resetting of the thirst threshold. AVP, arginine vasopressin; DI, diabetes insipidus; NA, not applicable.

One of the most severe forms of central DI results from destruction of the osmoreceptors that stimulate neurohypophyseal secretion of AVP. Studies in animals indicate that the primary osmoreceptors that control thirst and the secretion of AVP are located in the anterior hypothalamus in two circumventricular organs, the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT). Lesions in this region, termed the AV3V area, cause hyperosmolality through impaired thirst and impaired osmotically stimulated secretion of AVP[48,49]. The SFO has been implicated in the reciprocal control of appetite for sodium and water[50]. Because of the profound thirst deficits found in most of these patients, this condition is often termed adipsic central DI[51]. All reported cases have been due to osmoreceptor destruction to various extents and are associated with a range of different brain lesions (TABLE 1). Although many of these lesions are of the same type as those that cause central DI (FIG. 2), they usually occur more rostrally in the hypothalamus, consistent with the location of the primary osmoreceptor cells in the anterior hypothalamus. Adipsic hypernatraemia without hypothalamic lesions, accompanied by autoantibodies to the SFO, is a new, well-described disease in four young patients with hypernatraemia, no thirst and low vasopressin response to hypertonicity. Whereas structural abnormalities of the hypothalamic area are easily visible by MRI in classical adipsic hypernatraemia, no hypothalamic structural lesions could be identified in these patients. Specific circulating antibodies reactive to the mouse SFO and the sodium channel Na_x were present in the serum of all four patients. Mice injected with an immunoglobulin fraction of the patient's serum showed abnormalities in water and sodium homeostasis, vasopressin release and diuresis, which resulted in hypernatraemia[52].

Hereditary central DI. Familial neurohypophyseal DI (FNDI; also known as hereditary central DI) comes in many forms (TABLE 1) that are differentiated by the inheritance pattern and the underlying genetic lesion, which include mutations in *AVP*, *WFS1* and *PCSK1* (encoding proprotein convertase subtilisin/kexin type 1)[53]. PCSK1 is involved in processing numerous hypothalamic and digestive prohormones and *PCSK1* mutations can result in severe malabsorptive diarrhoea, growth hormone deficiency, central hypothyroidism, central hypogonadism and central hypocortisolism; ~80% of patients with these mutations show clinical signs of central DI[54]. Autosomal dominant FNDI is caused by >70 different mutations in different parts of the AVP gene, none of which occur in the copeptin moiety. Despite the wide range of mutations, patients with autosomal dominant FNDI have remarkably similar presentations. All heterozygous infants are healthy at birth and show no signs of DI but develop complete DI at a later age, which seems to vary depending on the mutation. Later age of onset (up to young adulthood) occurs in carriers with mutations in the signal peptide, whereas onset occurs in infancy for carriers with mutations in the AVP carrier neurophysin II[2], which is produced by cleavage of the AVP preprohormone. The mechanism underlying the 'dominant-negative' effect of autosomal dominant FNDI mutations is controversial but most evidence suggests that mutant AVP prohormone is retained in the endoplasmic reticulum (ER) of magnocellular neurons. Mutant AVP and functional AVP protein 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 ER-associated degradation (ERAD)[55]. This model helps explain results obtained in some mouse models of DI with human proAVP mutations, in which AVP-producing neuronal cell death was not observed at disease onset and was thus not thought to have a role in disease initiation[56].

Autosomal recessive FNDI is a rare disorder caused by mutations in *AVP* (types a and b) or other genes (types c and d) (TABLE 1). The clinical phenotype differs from that in autosomal dominant FNDI in several ways, including age of onset, plasma AVP levels during fluid deprivation, interfamily and intrafamily variation, and co-morbidity with other symptoms. The most common form of autosomal recessive FNDI, type c, is due to mutations in *WFS1*, as a clinical manifestation in Wolfram syndrome. X-linked recessive FNDI has been reported in one kindred with a classical FNDI phenotype, and has been mapped to Xq28, although the responsible gene or genes have not yet been identified[57].

Genetic evaluation of patients with suspected inherited central DI is fairly simple in most patients and should be considered in those with a positive family history of DI or with idiopathic forms of DI that appear at a young age[58,59].

Nephrogenic DI

AVP-regulated water permeability is a central component of the renal urine-concentrating mechanism. In diuretic kidneys in which AVP is low or absent, the collecting duct is water impermeable and dilute urine is produced. In antidiuretic kidneys, AVP levels are increased and the collecting duct becomes water-permeable due to increased levels of the water channel AQP2 in the apical membrane of principal cells resulting from exocytosis of AQP2-containing subapical vesicles[60]. Urine becomes concentrated as water is transported osmotically from the lumen of the collecting duct into the renal interstitium, which is hyperosmolar as a consequence of the renal countercurrent multiplication and exchange mechanisms. The basolateral cell membrane is constitutively water-permeable due to expression of the water channels AQP3 and/or AQP4. AVP binding to AVPR2 at the basolateral membrane of principal cells results in cAMP production by adenylyl cyclase 6 (REF.[61]) and activation of protein kinase A, which leads to phosphorylation of AQP2 and proteins involved in AQP2 exocytosis[62,63] (FIG. 3a). Although this basic mechanism is supported by considerable data, questions remain about mechanisms of apparent AVPR2-dependent but cAMP-independent AQP2 trafficking, and the role of non-vasopressin modulators of AQP2 trafficking, such as prostaglandin E2, nitric oxide and adenosine. Nephrogenic DI is caused by reduced renal sensitivity to the antidiuretic effect of physiological levels of AVP[3], owing to an acquired or genetic defect in renal mechanisms for urine concentration.

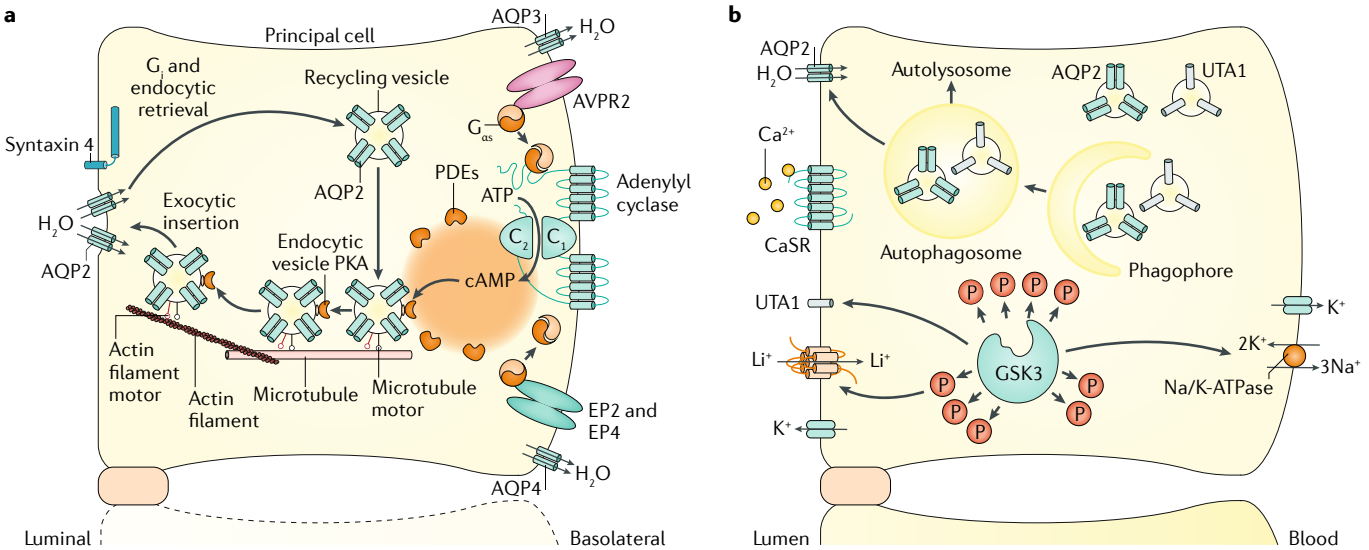

Fig. 3 | **Pathogenetic mechanisms in nephrogenic DI. a** | Mechanism of arginine vasopressin (AVP)-stimulated osmotic water permeability in principal cells of the collecting duct. AVP binding to the G protein-coupled receptor AVP receptor 2 (AVPR2) results in increased production of cAMP by adenylyl cyclase 6, thereby activating protein kinase A and inducing phosphorylation of target proteins, including the water channel aquaporin 2 (AQP2). These phosphorylations promote fusion of AQP2-containing vesicles with the apical plasma membrane of the principal cells, and thereby increased AQP2 levels, resulting in increased water uptake from the urine. The basolateral plasma membrane expresses AQP3 and AQP4, making it constitutively water-permeable. **b** | Mechanisms of nephrogenic diabetes insipidus (DI) caused by lithium, hypokalaemia and hypercalcaemia or hypercalciuria. Entry of lithium into the principal cell inhibits glycogen synthase kinase 3β (GSK3β), reducing expression of AQP2 (which forms tetramers). Hypokalaemia and hypercalcaemia or hypercalciuria cause autophagy-mediated degradation of monomeric AQP2 and UTA1. Hypercalciuria may activate the calcium-sensing receptor (CaSR), which increases intracellular Ca^{2+} levels and enhances basal autophagy by one or more mechanisms. Autophagy is initiated by the formation of phagophores, which engulf AQP2, UTA1 and other cytoplasmic proteins (including junctional and cytoskeletal proteins), as well as dysfunctional organelles (such as damaged mitochondria). Phagophores elongate and close to generate double-membrane autophagosomes, which then fuse with lysosomes to form single-membrane autolysosomes, thereby delivering cargo for degradation. As a result, decreased abundance of AQP2 and UTA1 leads to impaired urinary concentrating ability. Part **a** adapted from REF.[3], Springer Nature Limited. Part **b** adapted with permission from REF.[74], Elsevier.

Acquired nephrogenic DI. Acquired nephrogenic DI is much more common than hereditary nephrogenic DI, is rarely severe and polyuria and polydipsia are moderate (3–4 l/day). The inability to generate a maximal urine osmolality results from resistance to the action of AVP in the collecting tubules or interference with the countercurrent mechanism secondary to medullary injury or to decreased sodium chloride reabsorption in the medullary thick ascending limb of the loop of Henle.

Lithium administration is the most common cause of acquired nephrogenic DI — 19% of 1,105 unselected patients on chronic lithium therapy had polyuria (>3 l/day)[64]. Lithium treatment causes reduced AQP2 expression and altered trafficking in the short term and loss of principal cells in the long term[65,66]. Lithium-induced AQP2 downregulation is probably a consequence of ENaC-mediated influx of lithium into principal cells, as collecting-duct-specific αENaC deficiency prevents the development of lithium-induced nephrogenic DI[67]. Lithium inhibits glycogen synthase kinase 3 (GSK3) signalling pathways[68,69] (FIG. 3b). Both GSK3 isoforms, GSK3α and GSK3β (encoded by *GSKA* and *GSK3B*, respectively), are inhibited by lithium, both directly and indirectly, by increased phosphorylation of Ser9 in GSK3β and Ser21 in GSK3α[70]. Other GSK3 inhibitors also reduce AQP2 expression in collecting duct cells in vitro, and ablation of *Gsk3a* or *Gsk3b* in mice causes polyuria[70]. Inhibition of GSK3β by lithium increases the expression of cyclooxygenase 2 and the local excretion of prostaglandin E2 (REF.[71]), which may counteract vasopressin action by causing endocytic retrieval of AQP2 from the plasma membrane. The urinary concentration of lithium in patients on well-controlled lithium therapy is sufficient to have this effect.

Other causes of transient acquired nephrogenic DI include hypercalcaemia, hypercalciuria and obstructive uropathy. In patients with obstructive uropathy, the observed suppression of AQP2 expression might be mediated by hydrostatic pressure[72]. Autophagic degradation of AQP2 is implicated in nephrogenic DI induced by hypokalaemia and hypercalcaemia[73,74] (FIG. 3b). Hypokalaemia and hypercalcaemia or hypercalciuria affect water permeability through regulating autophagic degradation of water and urea channels (FIG. 3).

Hereditary nephrogenic DI. Mutations in *AVPR2* (located at Xq28 and encoding a G-protein-coupled receptor) cause X-linked hereditary nephrogenic DI, resulting in complete vasopressin insensitivity in affected males[75,76]. More than 250 mutations in *AVPR2* have been identified, including missense mutations, nonsense mutations, deletions and insertions[10]. Mutations that

result in the production of a full-length protein are most common, although these mutant proteins are misfolded and are targeted for ERAD.

Mutations in *AQP2* (located at 12q13 and encoding the water-selective transporter AQP2) cause hereditary autosomal nephrogenic DI[77]. Of the ~65 disease-causing *AQP2* mutations identified, most are missense or nonsense mutations that cause autosomal recessive nephrogenic DI[78]. Some missense mutations result in the production of a mislocalized but functional water-transporting AQP2, whereas others result in severely misfolded proteins that are targeted for ERAD. Interestingly, a few mutations in the carboxyl terminus of *AQP2* result in autosomal dominant nephrogenic DI, probably because heterotetramers of mutant and wild-type AQP2 are retained in the Golgi, preventing their exocytosis[79].

Primary polydipsia

Primary polydipsia produces physiological suppression of AVP secretion by excessive water intake, and is thus the opposite of the secondary polydipsia that occurs in response to excessive water loss due to pathologically diminished AVP activity in other types of DI. The excessive intake in individuals with CWD is attributable to the sluggish drop in thirst that occurs immediately after water intake (oropharyngeal regulation) and their diminished osmotic set point for thirst (but not AVP)[80]. Actual water intake also seems to be greater at any level of thirst. The extent to which dipsogenic DI is distinct from CWD is unknown, although patients with dipsogenic DI have a higher osmotic set point for AVP and a higher plasma osmolality than those with CWD[34]. Hypothalamic sarcoidosis seems to disrupt the normal congruence of the set points in AVP and desire for water[81], and an analogous mechanism could operate in CWD.

Primary polydipsia occurs most commonly in patients with chronic schizophrenia. The discussion below compares these patients and the subset with PIP to matched non-polydipsic patients with schizophrenia. Because the increased water intake in polydipsic patients seems to be unrelated to thirst[25], it is assessed by asking patients about their 'desire for water' (in cups), which can be subsequently validated by a period of ad libitum drinking.

Immediately following water intake, desire for water drops acutely in polydipsic patients but then rapidly rebounds, indicating that an external factor overrides normal oropharyngeal suppression of water intake (FIG. 1). By contrast, plasma AVP exhibits the normal acute drop and does not abnormally rebound. The osmotic set point for 'desire for water' is diminished in polydipsic patients, whereas the increase in desire at higher levels of plasma osmolality is blunted, but only in the subset of patients with PIP (reviewed elsewhere[82]). The osmotic set point for AVP secretion is also diminished but only in the PIP subset and is further aggravated, in this subset alone, by acute psychological stress and psychotic exacerbations to a degree capable of inducing water intoxication (FIG. 4a). Thus, unlike other patients with primary polydipsia, the patient subset with PIP fail to appropriately suppress AVP.

These findings in polydipsic psychotic patients seem attributable to an anterior hippocampus-mediated disruption of hypothalamic function that may also contribute to their psychiatric illness[83]. Polydipsic patients with and without PIP exhibit discrete deformations on the surface of the anterior hippocampus, the part of the brain that is also most consistently implicated in the pathophysiology of schizophrenia. In polydipsic patients, these deformations are restricted to the anterior lateral surface, which projects to the anterior hypothalamus and normally restrains stress hormone secretagogue release from parvocellular neurons and AVP release from magnocellular neurons during psychological stress[84] (FIG. 2). Larger deformations are apparent in polydipsic patients with PIP than in those without PIP, whereas deformations in non-polydipsic patients are limited to the opposite (anterior medial) surface. AVP and stress hormone responses to psychological (but not physical) stress are greatest in the PIP subset of polydipsic patients, normal in non-PIP polydipsic patients and blunted in non-polydipsic patients compared with healthy individuals. Indeed, the extent of these deformations as well as those on the medial surface of the amygdala (which is also heavily implicated in schizophrenia and in hypothalamic regulation of neuroendocrine and diverse psychologically driven stress responses) are proportional to the AVP responses in the three patient groups.

These results support those of other studies showing that anterior hippocampus pathology in polydipsic patients induces a limbic-based stress diathesis[85] that underlies their water imbalance and features of their psychiatric illness. In particular, the anterior lateral hippocampal and medial amygdala deformations are also proportional to the level of oxytocin that is secreted from adjacent magnocellular neurons in the anterior hypothalamus, and normally promotes diverse social behaviours that are particularly impaired (contributing to negative psychotic symptoms) in those with polydipsia. Impairments in social cognition, and particularly fear, are proportional to oxytocin levels in patients with polydipsia and are ameliorated by intranasal oxytocin administration in those with polydipsia but not in those without polydipsia[83] (FIG. 4a).

Familial concordance supports a role for genetic factors in polydipsia, of which polymorphisms in the orexin 1 receptor are most compelling[86]. Why polydipsia would be a consequence of an anterior hippocampus-mediated stress diathesis is unclear, although similarities between the polydipsia and other stereotypic behaviours commonly found in this subset of patients and schedule-induced polydipsia (SIP) and other stereotypic behaviours seen in mammals with hippocampal lesions may be relevant[87]. SIP is enhanced by neuroendocrine dysfunction[88], is associated with other neural and functional changes commonly seen in individuals with schizophrenia[83,89], is probably an abnormal response to stress (that is, stress diathesis)[90] and, like the polydipsia in patients, is preferentially diminished by clozapine compared with other antipsychotic medications[62,91].

Technological advances have helped characterize how pre-systemic and even pre-ingestion factors that motivate water intake and enhance AVP secretion[92]

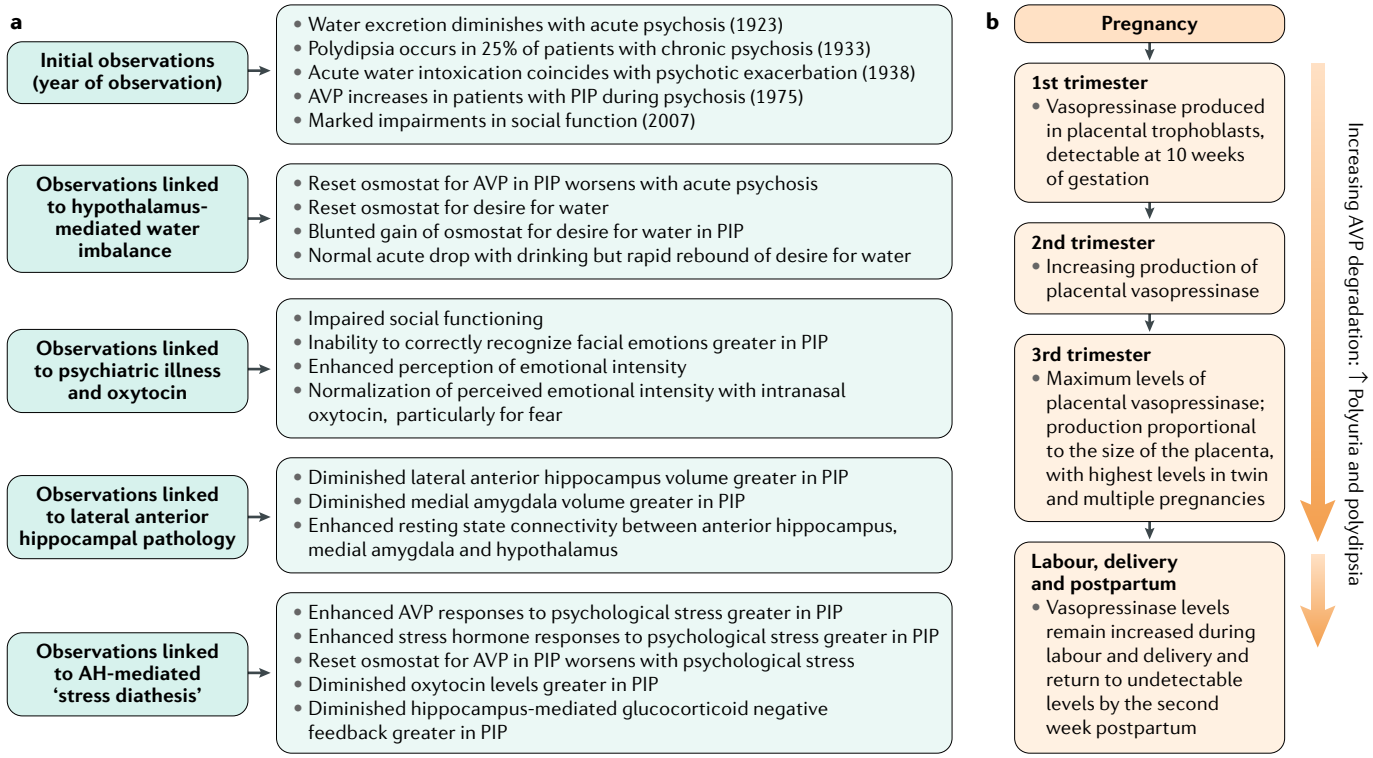

Fig. 4 | **Models of pathogenesis in primary polydipsia in schizophrenia and gestational DI. a** | Primary polydipsia. Findings pertain to schizophrenia patients with primary polydipsia with and without the psychosis intermittent hyponatraemia–polydipsia syndrome (PIP). The figure highlights the initial unexplained observations suggesting that the life-threatening water imbalance in patients with PIP was directly linked to their psychotic disorder, as well as subsequent studies that provide plausible pathophysiological mechanisms arising from disruption of recognized mammalian neural functions. The structural and functional findings support the view that the more-disrupted neuroendocrine function in patients with PIP than in non-PIP polydipsic patients is due to more-extensive pathological changes in the anterior lateral hippocampus, whereas non-polydipsic patients have structural changes on the anterior medial surface which do not interfere with their normal hippocampus-mediated compensatory neuroendocrine responses to chronic psychological stress. **b** | Gestational diabetes insipidus (DI) is caused by increased degradation of arginine vasopressin (AVP) by placental vasopressinase, which results in a presentation resembling that in central DI. Placental vasopressinase is produced by placental trophoblasts and is detectable by 10 weeks of gestation. Circulating vasopressinase levels increase about 300-fold over the following weeks, peaking in the third trimester, remain higher during labour and delivery and return to undetectable levels around the second week postpartum. AH, anterior hippocampus.

are integrated in the lamina terminalis, along with the better characterized osmotic, cardiovascular and circadian influences that regulate water balance[93,94] (FIG. 1). The anterior hippocampus-mediated stress diathesis could operate through this pathway and thus the ability to isolate its disruptive effects on water balance could reveal how it also disrupts hypothalamically modulated behaviours and effects that contribute to the psychotic disorder[95].

Gestational DI

Gestational DI is caused by increased degradation of AVP by the placental enzyme vasopressinase[96,97], which results in a presentation resembling that of central DI (FIG. 4b). Some patients may be predisposed to gestational DI as a result of pre-existing, subclinical AVP deficiency[98,99]. Vasopressinase is secreted by the kidneys and the liver[100]. During pregnancy, placental trophoblasts also produce vasopressinase, which is detectable at 10 weeks of gestation. Circulating placental vasopressinase levels increase ~300-fold over the following weeks (peaking in the third trimester)[36], remain high during labour and delivery and return to undetectable levels around the second week postpartum. The increased placental vasopressinase levels lead to increased degradation of AVP[101], although AVP levels remain in the normal range in the majority of pregnant women owing to increased AVP secretion by the posterior pituitary gland.

Diagnosis, screening and prevention

Clinical manifestations

Polyuria and polydipsia in DI and primary polydipsia do not necessarily differ in their specific manifestations, even though the underlying impairment of urinary concentrating mechanisms is different in the two conditions[102]. Compared with other forms of DI, patients with central DI more often describe nocturia and a sudden onset of symptoms, as urinary concentration can often be maintained fairly well until the residual neuronal capacity of the hypothalamus to synthesize AVP falls below 10–15% of normal capacity, after which urine output increases dramatically.

Patients with DI, especially those with underlying osmoreceptor defect syndromes, can also show varying degrees of dehydration and hyperosmolality if renal water losses cannot be fully compensated for by fluid intake. The resulting symptoms are due to dehydration (mostly cardiovascular symptoms, including hypotension, acute tubular necrosis secondary to renal hypoperfusion and hypovolaemic shock)[103,104] or hyperosmolality (mostly neurological symptoms that reflect the extent of brain dehydration as a result of osmotic water shifts from the intracellular compartment). Manifestations may range from non-specific symptoms, such as irritability and cognitive dysfunction, to more severe manifestations, such as disorientation, reduced level of consciousness, seizure, coma, focal neurological deficits and cerebral infarction[103,105].

Polyuria in children is defined as excretion of urinary volumes of >150 ml/kg/day in neonates, >100–110 ml/kg/day in children ≤2 years of age and >50 ml/kg/day in older children[7]. In children, central DI can often be accompanied by additional signs or symptoms, such as growth retardation, fatigue, headaches, emesis and visual field deficits, owing to intracranial neoplasms that affect CNS structures and other pituitary axes[9]. A strong preference for water in children with central DI (which limits the intake of more caloric liquids or solids) or associated growth hormone deficiency can slow weight gain and linear growth.

Differential diagnosis

Once hypotonic polyuria is confirmed, the next step is to distinguish between central DI, nephrogenic DI and primary polydipsia, which is crucial because treatment strategies differ and application of the wrong treatment can be dangerous[4]. However, reliable diagnosis is difficult[5], as many available tests are unsatisfactory[31] and often result in false diagnoses, especially in patients with primary polydipsia or partial, mild forms of central DI[1,6].

The indirect water deprivation test was the gold standard for differential diagnosis of polyuria–polydipsia syndrome for many years. This test is based on indirect assessment of AVP activity by measurement of the urine concentration capacity during a prolonged period of dehydration and again after a subsequent injection of an exogenous synthetic AVP analogue, desmopressin[106–108]. Interpretation of the test results is based on published recommendations[109]. If upon thirsting, urinary osmolality remains <300 mOsm/kg and does not increase by >50% after desmopressin injection, complete nephrogenic DI is diagnosed. Complete central DI is diagnosed if the urinary osmolality increase is >50% after desmopressin injection. In partial central DI and primary polydipsia, urinary concentration increases to 300–800 mOsm/kg, with an increase of >9% (in partial central DI) and <9% (in primary polydipsia) after desmopressin injection.

However, these published criteria are based on post hoc data from only 36 patients, who had a wide overlap in urinary osmolalities. Furthermore, the diagnostic criteria for this test were derived from a single study with post-hoc assessment[109] and have not been prospectively validated on a larger scale (reviewed elsewhere[4]). Consequently, this test has been shown to have considerable diagnostic limitations; overall diagnostic accuracy is 70%, and accuracy is only 41% in patients with primary polydipsia[6].

Several reasons exist for the disappointing diagnostic outcome of the indirect water deprivation test. First, chronic polyuria itself can affect renal concentration capacity, through renal washout[110–112] or downregulation of AQP2 expression in the kidneys[113], which may lead to a reduced renal response to osmotic stimulation or exogenous desmopressin[113] in different forms of chronic polyuria[109]. Second, in patients with AVP deficiency, urinary concentrations can be higher than expected[114,115], especially in those patients with impaired glomerular function[31,116,117], or can result from a compensatory increase in *AVPR2* expression in patients with chronic central DI[118]. Finally, patients with acquired nephrogenic DI are often only partially resistant to AVP, resulting in a clinical presentation that is similar to partial central DI.

To overcome these limitations of the indirect water deprivation test, direct measurement of AVP levels has been proposed to improve the differential diagnosis of polyuria–polydipsia syndrome. Indeed, in a 1981 study, patients with central DI were reported to have AVP levels below a calculated normal range (defining the normal relationship between plasma osmolality and AVP levels), whereas AVP levels were above the normal range in patients with nephrogenic DI and within the normal range in patients with primary polydipsia[119]. However, despite these promising initial results, this method has failed to enter routine clinical use for various reasons. First, several technical limitations of the AVP assay result in a high preanalytical instability of AVP in samples[115,120,121]. Second, the accuracy of diagnoses using commercially available AVP assays has been disappointing, with correct diagnoses in only 38% of patients with DI, and particularly poor differentiation between partial central DI and primary polydipsia[4,6]. Third, an accurate definition of the normal physiological range defining the relationship between plasma AVP levels and osmolality is still lacking, especially for commercially available assays[119,122,123], which is crucial to identify AVP secretion outside the normal range in patients suspected of having DI[6].

Copeptin, the C-terminal segment of the AVP prohormone, is an easy-to-measure AVP surrogate that is very stable ex vivo[120]. As the serum copeptin level reflects the osmosensitive circulating AVP concentration, it is a promising biomarker for differential diagnosis of polyuria–polydipsia syndrome. Two studies have shown that a basal copeptin level of >21.4 pmol/l without prior thirsting unequivocally identifies nephrogenic DI, rendering a further water deprivation test unnecessary in these patients[6,124]. The more difficult differentiation is between patients with primary polydipsia and those with central DI, especially mild forms. A study in 144 patients with central DI or primary polydipsia (the largest to date) directly compared the diagnostic accuracy of a hypertonic saline infusion and copeptin measurement with that of the indirect water deprivation test[102]. An osmotically stimulated copeptin level of >4.9 pmol/l

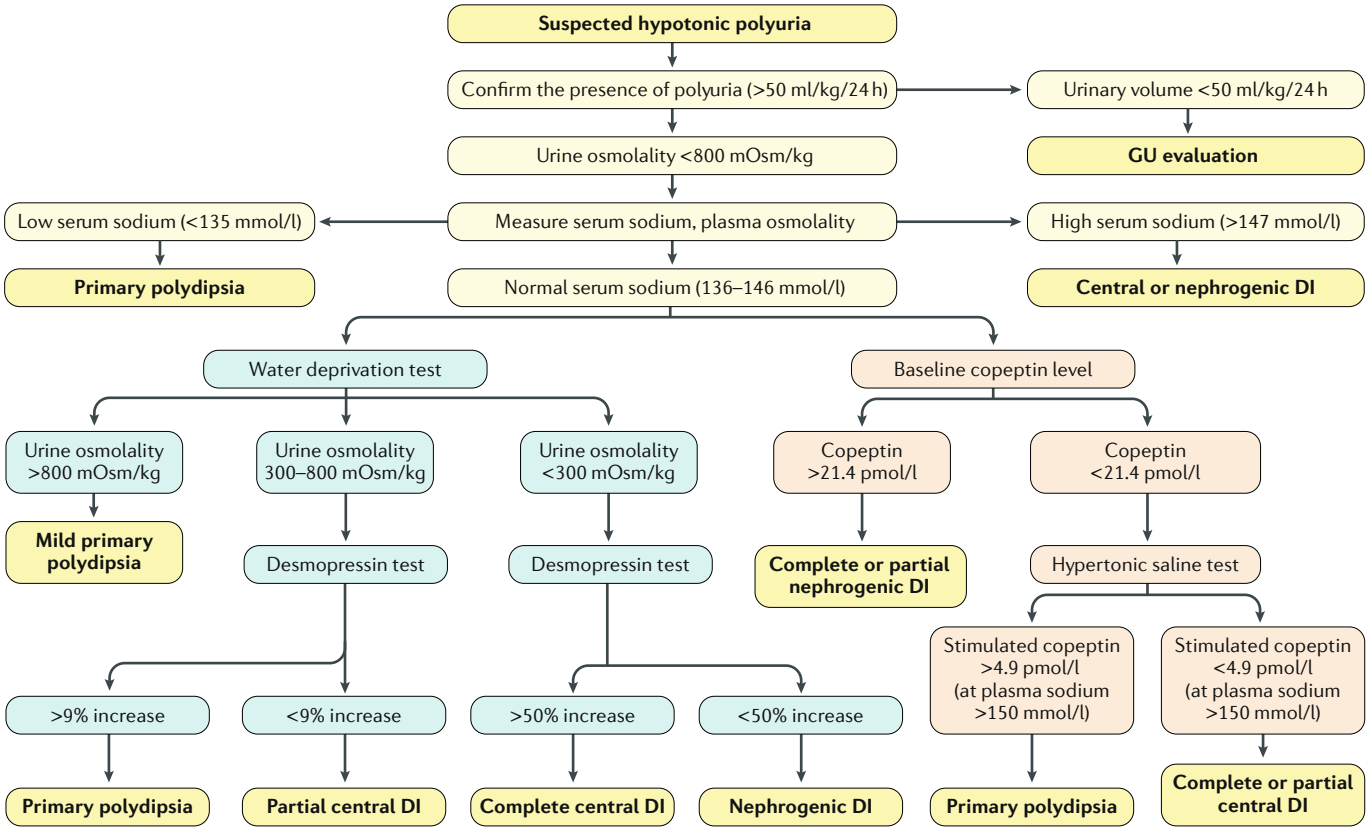

Fig. 5 | **Modified algorithm for differential diagnosis of polyuria–polydipsia syndrome.** In a first step, polyuria must be confirmed, otherwise polyuria–polydipsia syndrome is excluded and genitourinary (GU) evaluation is needed. In case of polyuria and a urinary osmolality <800 mOsm/kg, serum sodium and plasma osmolality are measured. If these levels are in the normal range, further differentiation is done using either a classical water deprivation test or a copeptin-based algorithm (if copeptin measurement is available). DI, diabetes insipidus. This figure is modified from Figure 1 from Gubbi, S., Hannah-Shmouni, F., Koch, C.A. & Verbalis, J.G. in Endotext (eds. Feingold, K.R. et al.). The link to the article on PUBMED can be found here: https://www.ncbi.nlm.nih.gov/books/NBK537591/ or at Endotext.org.

after infusion of 3% saline (aiming at a sodium level >150 mmol/l) had an overall diagnostic accuracy of 96.5% (93.2% sensitivity and 100% specificity) in distinguishing between patients with primary polydipsia and those with central DI, compared with only 76% for the indirect water deprivation test[102]. The addition of copeptin measurement did not improve the diagnostic performance of the indirect water deprivation test. By contrast, the overall diagnostic accuracy of the predefined ratio of Δcopeptin (0800–1600 h) to plasma sodium 1600 h in distinguishing between primary polydipsia and central DI was lower than that of the water deprivation test without copeptin, most likely due to the lack of osmotic stimulus and therefore the lack of a significant increase in AVP or copeptin by thirsting alone.

Taken together, these data indicate that plasma copeptin is a promising biomarker for differential diagnosis of polyuria–polydipsia syndrome and that hypertonic saline-stimulated copeptin measurement (using the modified diagnostic workflow in FIG. 5) will probably replace the water deprivation test as the diagnostic method of choice for hypotonic polyuria. However, importantly, the hypertonic saline infusion test requires close monitoring of sodium levels to ascertain a diagnostically meaningful increase in plasma sodium within the hyperosmotic range[125,126], while preventing a marked increase.

Of note, the copeptin test is currently not universally available, although copeptin assays are commercially available throughout Europe, Australia, India and Mexico. Registration for commercialization is currently pending in Taiwan, Korea and Canada. To date, the copeptin assay has no Clinical Laboratory Amendments certification in the USA but it is available as a research use only (RUO) test in two large service laboratories.

Radiological findings

Once the type of DI has been diagnosed, the underlying pathology must be identified. Gadolinium-enhanced MRI of the sella and suprasellar regions is used to check for anatomical disruption of the pituitary or hypothalamic anatomy by, for example, macroadenoma, empty sella, infiltrative diseases or metastases. Assessment of the posterior pituitary gland and the pituitary stalk by unenhanced brain MRI can sometimes be useful for differential diagnosis of DI. An area of hyperintensity, referred to as the PBS, is observed in healthy individuals in the posterior part of the sella turcica in sagittal T1-weighted images[127], and is thought to result from the T1-shortening effects of stored AVP in neurosecretory

granules in the posterior pituitary gland[128]. Although earlier small-scale studies demonstrated the presence of the PBS in healthy individuals and its absence in patients with central DI[129], subsequent larger studies showed an age-related absence of a PBS in 52–100% of healthy individuals[130]. Conversely, a persistent PBS detected in some patients with central DI[9,131] could be because the disease is at an early stage or could reflect oxytocin stores rather than stored AVP. The PBS has been reported to be absent in some patients with nephrogenic DI and present in others[132]. In a large prospective observational study in 92 patients with polyuria–polydipsia syndrome, brain MRI revealed the presence of the PBS in only 39% of patients with primary polydipsia but in 70% of patients with central DI[102]. Consequently, the presence or absence of the PBS on MRI is not sufficient to establish a diagnosis in patients with DI.

A similar caveat applies to imaging-based assessment of the pituitary stalk: a diameter of >2–3 mm is generally considered to be pathological[133] (for example, in hypophysitis, granulomatous disorders, tuberculosis, craniopharyngioma, germinoma or metastasis to the sella or suprasellar region[134]) but is not necessarily specific for idiopathic central DI[102,135]. However, if scans reveal thickening of the stalk with the absence of the PBS, then a diligent search for neoplastic or infiltrative lesions of the hypothalamus or pituitary gland is indicated[136].

Diagnostic evaluation of DI during pregnancy is challenging. Baseline investigation should involve a complete blood count, liver and kidney values, electrolyte levels (including serum calcium) and serum and urinary glucose and osmolality. The water deprivation test is not recommended during pregnancy due to the high risk of dehydration and, consequently, utero-placental insufficiency[137]. Also, copeptin measurement has never been prospectively evaluated for DI diagnosis in pregnant patients. Importantly, measurement of osmotically stimulated copeptin levels in pregnancy cannot be recommended. In view of the generally lower serum sodium levels during pregnancy, AVP-deficient DI can be diagnosed in women with an increased sodium level of >140 mmol/l and inadequately diluted urine (urine osmolality <300 mOsm/l)[138]. In all other cases, an overnight water deprivation test may be considered, provided the woman is not at risk of dehydration (severe polyuria, serum sodium >140 mmol/l or serum osmolality >290 mOsm/kg). An increase in urine osmolality to >600 mOsm/l after an overnight water deprivation test argues against clinically relevant DI, although evidence for this cut-off is lacking. In patients with urine osmolality <600 mOsm/l, careful evaluation of patient history, onset of symptoms and presentation is recommended for further differentiation. Cerebral imaging by MRI during pregnancy is only recommended if DI secondary to haemorrhage, neoplasia or trauma is suspected[4].

Diagnosis of DI in children

Once polyuria is established in children, laboratory measurement of serum osmolality, serum sodium, urine osmolality, urine specific gravity and potassium, glucose and calcium is necessary to exclude diabetes mellitus or nephrogenic DI induced by hypercalcaemia or hypokalaemia. Concomitant serum osmolality >300 mOsm/kg and urine osmolality <300 mOsm/kg is indicative of DI[139]. By contrast, a patient with urine osmolality >600 mOsm/kg is unlikely to have DI. If urine osmolality is intermediate and clinical suspicion of DI remains, a diagnosis is confirmed using a water deprivation test carried out in a closely monitored medical setting (not at home). Special caution is needed in neonates, who have a high risk of dehydration. Hypertonic saline tests in children are not recommended (of note, the algorithm in FIG. 5 is not validated for children).

In children with central DI, hormonal deficiencies or excess of other pituitary axes must be assessed and MRI of the sella carried out (see above). In children with nephrogenic DI, medication history must be evaluated and electrolyte abnormalities excluded and a search for underlying acute or chronic renal diseases conducted. For both central DI[140] and nephrogenic DI, if symptom onset occurs in early childhood, congenital causes must be evaluated even if most cases are idiopathic, especially in the absence of a family history. In children with primary polydipsia, careful psychiatric evaluation and medication history are important. Hypothalamic diseases that could lower thirst threshold must be taken into account. A child may also habitually drink large volumes of water without any organic cause[140].

Prevention

Currently, most forms of DI cannot be prevented. The incidence of postoperative DI seems to be dependent mainly on hospital and surgeon case-load, suggesting that greater experience leads to lower rates of postoperative DI[141]. To date, the prevalence of postsurgical DI seems to be similar for endoscopic trans-sphenoidal surgery and microscopic trans-sphenoidal surgery of large pituitary adenomas[142]. Perioperative hydrocortisone treatment influences the rate of postoperative DI[143]. Administration of hydrocortisone doses lower than the usual institution's standard protocols led to almost 50% lower incidence of DI, possibly owing to suppression of AVP release by hydrocortisone. Prevention of lithium-induced nephrogenic DI is an important aspect of the treatment of affective disorders. In patients receiving long-term lithium treatment, nephrogenic DI seems to only be partially reversible after discontinuation of lithium[144]. Close monitoring of lithium treatment is recommended, including annual measurement of the urinary volume per day to make both the patient and the physician aware of the development of drug-induced nephrogenic DI. As gestational DI is rare and there is no straightforward diagnostic measure for this disorder, screening in pregnancy is not helpful.

Management

The general goals of treatment for all forms of DI include correcting pre-existing water deficits and reducing ongoing excessive water loss through urination. The specific therapy that is required will depend on the type of DI and the clinical circumstances. Management of primary polydipsia entails different challenges and solutions because therapies are primarily based on

behavioural interventions rather than biological and pharmacological interventions.

Correction of body water deficits

Untreated central and nephrogenic DI often leads to hyperosmolar dehydration. In a hyperosmolar patient, the total body water deficit can be estimated using the following formula:

$$\text{Total body water deficit} = 0.6 \times \text{premorbid weight} \times (1 - 140/[Na^+])$$

where $[Na^+]$ is the serum sodium concentration in millimoles per litre and weight is in kilograms.

To reduce the risk of brain damage from prolonged exposure to severe hyperosmolality, in adults, plasma osmolality should be lowered over the first 24 h of therapy by replacing ~50% of the calculated free water deficit. Physiologically, neurons increase intracellular osmolality by increasing the cellular content of organic osmolytes to protect against excessive osmotic shrinkage during prolonged hyperosmolality[145]. However, once synthesized, these osmolytes cannot be immediately dissipated, so correction to a normal plasma osmolality should be spread over the subsequent 24–72 h to avoid cerebral oedema from osmotic water shifts into the brain during treatment[146,147]. This approach is particularly important in children, as multiple studies in children have demonstrated that limiting correction of hypernatraemia to a maximum rate of 0.5 mmol/l/h prevents symptomatic cerebral oedema and seizures[148,149].

The choice of appropriate fluid replacement is crucial, as treatment of hyperosmolar dehydration with isotonic saline is dangerous because it can result in worsened hypernatraemia[150]. In patients with central or nephrogenic DI, the urine is essentially pure water. A child weighing 10 kg has an estimated 7 l of total body water. Administration of 1 l of isotonic saline (154 mmol Na^+) with excretion of 1 l of hypotonic urine containing 10 mmol Na^+ will result in retention of 144 mmol Na^+, and thus will increase serum sodium concentration by 20 mmol/l (144 mmol/7 l). In these patients, isotonic fluids should only be administered for acute intravascular volume expansion in those with hypovolaemic shock, which is an exceptionally rare complication, as extracellular fluid volume is usually preserved with hyperosmolality. Patients with DI should be treated with hypotonic fluids, either milk or water consumed enterally or, if required, 5% dextrose in water administered intravenously. The administration of hypotonic fluids as an intravenous bolus is not recommended; instead, the infusion rate should be adjusted to exceed the hourly urine output by an amount necessary to achieve the desired reduction in the calculated total body water deficit. The aim is to provide just enough water to safely normalize serum sodium concentration at a rate of <0.5 mmol/l/h (<10–12 mmol/l/day)[151] or even slower so as to prevent cerebral oedema and, potentially, death[147]. As 5% dextrose in water provides no osmotic load, urine output can decrease substantially, highlighting the importance of monitoring fluid balance to avoid rapid swings in serum sodium concentration. Frequent, careful monitoring of the clinical condition and biochemistry is crucial for safe treatment and requires a clinical setting with the necessary experience in treating complicated electrolyte disorders.

To enable fluid intake to be correctly regulated by thirst physiology, oral consumption of fluids should begin as soon as feasible. In most patients with DI, thirst remains intact and patients will drink sufficient fluid to maintain a fairly normal fluid balance. Specific treatments for different types of DI are discussed separately below.

Central DI

Patients with central DI should be treated to reduce polyuria and polydipsia to levels that allow maintenance of a normal lifestyle. As the goal of therapy is improved symptomatology, the prescribed regimen should be individually tailored to individual patients to address their needs. The safety of the therapeutic regimen and avoidance of detrimental effects of overtreatment are primary considerations, as in most patients, central DI has a fairly benign course.

Fluid administration. Patients with central DI will develop thirst when the plasma osmolality increases by 2–3%[1], unless the hypothalamic osmoreceptors are also affected by the primary lesion that causes adipsic DI. Consequently, severe hyperosmolality is not a risk in patients who are alert, ambulatory and able to drink in response to perceived thirst. Although inconvenient and lifestyle-disrupting, polyuria and polydipsia are not life-threatening. However, hyponatraemia does not cause specific symptoms initially and can quickly progress to more symptomatic levels if fluid intake continues during continuous antidiuresis. Therefore, treatment of central DI should be designed to minimize polyuria and polydipsia without causing undue risk of hyponatraemia as a result of overtreatment.

Pharmacological therapy. Although different agents have been used in the past (for example, chlorpropamide and pitressin tannate), desmopressin is the current standard of care for patients with central DI[152], owing to its long half-life, selectivity for AVPR2 and the availability of multiple preparations. The optimal dose and dosing intervals should be determined for each patient. Oral preparations provide greater convenience and are usually preferred by patients. However, starting with a nasal spray initially is preferable because of greater consistency of absorption and physiological effect, after which the patient can be switched to an oral preparation. After trying both preparations, patients can then choose which they prefer for long-term treatment. The duration of action of individual doses should be ascertained in each patient owing to variability in responses between patients[153]. A satisfactory schedule can generally be determined using modest doses of desmopressin. The maximum dose of desmopressin required rarely exceeds 0.2 mg orally, 120 μg sublingually or 10 μg (one nasal spray) two or three 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[154]. Once-daily dosing can sometimes suffice, although this is rare. In some patients, the effect of intranasal or oral desmopressin is erratic, due to interference with absorption from the gastrointestinal tract or nasal mucosa. Administration of oral desmopressin on an empty stomach[155] or intranasal desmopressin after cleansing of the nostrils can reduce this variability and prolong the duration of action. Desmopressin resistance due to antibody production has not been reported.

Hyponatraemia is the major complication of desmopressin therapy — a 27% incidence of mild hyponatraemia (serum Na^+ 131–134 mmol/l) and a 15% incidence of more severe hyponatraemia (serum Na^+ ≤130 mmol/l) have been reported after long-term follow-up of patients with chronic central DI[156]. Hyponatraemia usually occurs if the patient is continually antidiuretic while continuing normal fluid intake. Severe hyponatraemia from desmopressin treatment can be avoided by frequent monitoring of serum electrolyte levels during initiation of therapy. Patients who develop a low serum sodium concentration and do not respond to recommended decreases in fluid intake should be directed to delay a scheduled dose of desmopressin once or twice weekly until polyuria recurs, thereby allowing excess retained fluid to be excreted. Because desmopressin-induced hyponatraemia is usually chronic (>48 h duration), care must be taken in acutely treating these patients to avoid osmotic demyelination syndrome (ODS), a demyelinating disease of motor neurons that occurs when correction of serum sodium levels occurs too quickly. Current guidelines recommend limiting corrections to <12 mmol/l in the first 24 h and <18 mmol/l in the first 48 h (REF. [157]). Because cessation of desmopressin results in a rapid water diuresis ('aquaresis') once the drug is excreted by the kidneys, these patients can correct their hyponatraemia exceedingly quickly, putting them at high risk of ODS. Consequently, some authors recommend continuing to administer desmopressin while correcting the hyponatraemia at a controlled rate using hypertonic (3%) NaCl[158]. Alternatively, desmopressin can be re-administered to shut off an ongoing aquaresis once a desired correction of serum sodium (6–8 mmol/l) has been achieved. Whichever method is chosen, these patients must be monitored closely to avoid potentially catastrophic outcomes[159].

Central DI occurs frequently after surgery in the suprasellar region of the hypothalamus[160]. After confirmation of a central DI diagnosis, the best pharmacological therapy is desmopressin. However, because water overload with subsequent brain oedema is a concern after this type of surgery, treatment with oral or intravenous fluid replacement alone for long periods of time sometimes precedes the initiation of desmopressin therapy. If the patient is awake and responds to thirst, then thirst is a sufficient guide for water replacement. However, fluid balance must be maintained using intravenous fluids if the patient cannot respond to thirst because of a decreased level of consciousness or from damage to the hypothalamic thirst centre. Urine osmolality and serum sodium concentration should be checked every 4–6 h during initial therapy and then daily until stabilization or resolution of the DI. Caution is warranted regarding the volume of water replacement, as administration of excess water during continued administration of AVP or desmopressin can potentially cause hyponatraemia. Studies in animals suggest that desmopressin-induced hyponatraemia impairs survival of AVP-producing neurons after pituitary stalk compression[161], suggesting that over-hydration resulting in decreased stimulation of neurohypophyseal neurons might increase the probability of permanent DI.

Postoperatively, desmopressin can be administered parenterally (subcutaneously, intramuscularly or intravenously). Intravenous administration is generally preferred, as it precludes concerns about absorption, does not have significant pressor activity and the total duration of action is the same as with the other parenteral routes. The antidiuretic effect of desmopressin should occur promptly and typically lasts 6–12 h. Urine osmolality and volume should be monitored to ascertain whether the dose was effective and serum sodium concentration measured frequently (every 4–6 h) to ensure improvement in hypernatraemia. Allowing a return of polyuria is advisable before administration of additional doses of desmopressin because postoperative DI is often transient, and return of endogenous AVP secretion will become apparent by the absence of return of the polyuria. In addition, transient postoperative DI is sometimes part of a triphasic pattern following pituitary stalk transection (discussed above). Therefore, allowing recurrence of polyuria before re-dosing with desmopressin will enable earlier detection of a potential second phase of inappropriate antidiuresis and reduce the probability of severe hyponatraemia occurring as a result of continuing antidiuretic therapy and intravenous fluid administration when it is no longer required[162].

Patients with hypernatraemia due to osmoreceptor dysfunction (adipsic central DI) should be treated acutely with the same treatment as any hyperosmolar patient. The long-term management of osmoreceptor dysfunction syndromes requires that potentially treatable causes are investigated thoroughly, with measures to prevent dehydration instituted at the same time. Because hypodipsia cannot be cured, although spontaneous improvement occurs rarely, education of the patient and the patient's family about the importance of regulating fluid intake according to hydration status is the focus of management[163]. This can be accomplished most efficaciously by establishing a daily schedule of fluid intake regardless of the patient's thirst, which can be adjusted in response to changes in body weight[164]. As these patients will not drink spontaneously, daily fluid intake must be prescribed. If the patient has polyuria, desmopressin should also be prescribed, as in any patient with central DI. The success of fluid prescription should be monitored periodically (weekly at first, later every month, depending on the stability of the patient) by measuring serum sodium concentration. In addition, periodic recalculation of the target weight (at which hydration status and serum sodium concentration are normal) might be required to account for growth in children or body fat changes in adults.

Guidelines for pharmacological therapy of central DI in paediatric patients are not substantially different from

those in adults, except that oral or intranasal administration may be more difficult in very young patients, who may need to be treated with parenteral (subcutaneous) desmopressin for a period of time.

Nephrogenic DI

As bypassing a non-functional AVPR2 receptor or inserting functional water channels into the basolateral membrane of principal cells of the collecting duct are not presently feasible, current approaches for treatment of hereditary nephrogenic DI focus on ameliorating the symptoms instead of curing the disease. Treatment of acquired nephrogenic DI should target the underlying cause; for example, relief of urinary obstruction or amiloride therapy in lithium-associated nephrogenic DI. If these approaches are not possible, then treatment of acquired nephrogenic DI is the same as that for hereditary nephrogenic DI.

Diet. Dieticians have a crucial role in managing patients with nephrogenic DI in the first year of life, when fluid intake and caloric consumption are coupled. Osmotic load should be minimized while ensuring recommended caloric and protein intake to enable normal growth and development. As 1 g of table salt provides an osmolar load of ~34 mOsm (17 mOsm Na^+ and 17 mOsm Cl^-), the obligatory urine output in a patient with a urine osmolality of 100 mOsm/kg is increased by 340 ml for each gram of salt ingested. The dietary osmolar load can be estimated by multiplying the millimolar amounts of sodium and potassium by two (to account for the accompanying anions) and adding the gram amount of protein multiplied by four.

Pharmacological therapy. For patients on long-term lithium therapy, amiloride prevents uptake of lithium in the collecting duct epithelial cells and thus the inhibitory effects of intracellular lithium on water transport[165]. Hydrochlorothiazide has been shown to reduce urine output in both central and nephrogenic DI[166,167]. Thiazides decrease salt reabsorption by inhibiting the thiazide-sensitive co-transporter SLC12A3 in the distal tubule. The sodium loss reduces plasma volume, so that less water is presented to the collecting duct and lost in the urine. Also, hydrochlorothiazide administration reduced urine volume in *Slc12a3*-knockout mice with lithium-induced nephrogenic DI, suggesting a SLC12A3-independent mechanism of thiazide-mediated reduction in urine output[168]. Furthermore, inhibition of carbonic anhydrase by hydrochlorothiazide in the proximal tubule might reduce proximal sodium uptake and, via tubulo-glomerular feedback, reduce glomerular filtration. The carbonic anhydrase inhibitor acetazolamide reduces inulin clearance and cortical expression of sodium/hydrogen exchanger 3 and attenuates the increased urinary PGE2 levels observed in mice with lithium-induced nephrogenic DI[169], and is effective in humans with lithium-induced nephrogenic DI[170]. Polyuria in these patients is usually moderate (<6 l/day) and can be decreased by a strict clamping of the plasma lithium concentration at 0.8 mEq/l, a low-sodium diet and amiloride administration. Frequent plasma lithium measurements should be made when instituting a low-sodium diet and amiloride treatment, as an increase in lithaemia might be observed with the necessity to immediately decrease the lithium dosage.

In an animal model of nephrogenic DI, the use of the NSAID indomethacin reduced water diuresis independently of AVP[171]. A similar effect of prostaglandin synthesis inhibitors was later reported in patients with nephrogenic DI[172]. Since these early studies, prostaglandin synthesis inhibitors have become an essential component of the management of nephrogenic DI, particularly in the first years of life when management is most complicated. These drugs can have quite marked effects when first administered. Indeed, rapid reduction in plasma sodium levels following the initiation of indomethacin and hydrochlorothiazide therapy can induce hyponatraemic seizures[173]. Patients with hereditary partial nephrogenic DI typically carry mutations that result in partial function of either AVPR2 or AQP2, and their urine osmolality may increase after desmopressin treatment[174,175].

Hypercalcaemic and hypokalaemic nephrogenic DI manifestations are usually of mild to moderate severity and are easily reversed by normalization of plasma calcium or potassium levels.

Primary polydipsia

Management of primary polydipsia depends on the psychological profile of the patient and whether there is concurrent hyponatraemia. Often, no effective treatment is available, leaving patients at risk of structural urinary tract abnormalities and other medical complications that may contribute to a reduced lifespan.

Pharmacological therapy. The most acute danger of primary polydipsia is episodic water intoxication, which occurs in psychotic patients with PIP. This subset of polydipsic patients exhibits a reset osmostat for AVP that drops to levels consistent with water intoxication during acute psychotic episodes. Symptomatic hyponatraemia in other patients with polydipsia usually occurs because of medications that impair renal diluting capacity. AVPR2 antagonists rapidly normalize serum sodium concentration in these patients, but they require close monitoring to avoid dehydration and renal damage[176]. Unlike other antipsychotic agents, clozapine seems to normalize sodium levels in patients with PIP who are at risk of water intoxication, although none of the published studies were placebo-controlled and this drug carries unique, potentially life-threatening risks[12]. Clozapine's effects seem to be attributable to decreased fluid intake rather than increased fluid excretion[177], and thus may prove effective in normonatraemic psychotic polydipsic patients as well, assuming that the risks are justified.

Many other treatments have been inconclusive or ineffective in treating polydipsia or impaired water excretion in psychotic patients, including consuming electrolyte-containing beverages, reducing the dose or switching to another antipsychotic agent, and adding angiotensin inhibitors, α-adrenergic or β-adrenergic receptor antagonists, or opioid antagonists[178]. Case

reports suggest that acetazolamide can reduce polydipsia, and these observations may warrant further study[179]. Unlike psychotic disorders, CWD typically resolves with successful pharmacological treatment of the core psychiatric symptoms (such as depression and anxiety). Desmopressin is generally contraindicated in patients with primary polydipsia because of increased risk of hyponatraemia. However, in patients with dipsogenic DI, the water intake in at least some patients seems to be driven primarily by a reduced osmotic threshold for thirst, and desmopressin treatment has been successful, presumably by reducing plasma osmolality below the set point for thirst. Of particular interest is a case of central DI in a patient with schizophrenia whose polydipsia was successfully treated with desmopressin following behavioural therapy of concurrent primary polydipsia[180].

Behavioural therapy. Monitoring diurnal weight gain can prevent water intoxication in patients with PIP. Based on pre-determined increases that are predictive of incipient water intoxication (generally 5–8 kg increase in body weight) or the presence of prodromal signs, a brief fluid restriction (1–3 h) is imposed; this procedure should only be carried out in closely monitored settings because of the risk of over-correction in patients with chronic hyponatraemia. Standard behavioural treatments, such as relaxation, response prevention, cognitive behavioural therapy and token economies, have been used successfully to supplement medication in psychiatric patients or as stand-alone treatments in those without a psychiatric disorder, and would most likely be effective in individuals without an Axis I psychiatric disorder who have become habitual compulsive water drinkers.

Diet. Ice chips can help reduce polydipsia, perhaps by acting through recognized thermoregulatory mechanisms and specifically oropharyngeal influences on the subfornical organ in the lamina terminalis[93]. In some patients with primary polydipsia, hard candies (such as lemon drops) can be used to increase salivary flow and decrease the dry mouth sensation that leads to increased fluid ingestion.

Gestational DI

Once diagnosis of gestational DI is confirmed, treatment with desmopressin is indicated, regardless of whether DI is permanent or transient[152]. Although trial data are lacking, no adverse maternal or fetal effects from desmopressin have been reported[181]. Despite structural similarities to oxytocin, desmopressin administered intranasally had no effect on induction of labour[15]. Desmopressin is not affected by the placental vasopressinase[181]. Initiating treatment with the lowest desmopressin dosage at bed time to prevent nocturia is recommended. The dose is then slowly titrated upwards according to symptoms and under regular control of serum sodium levels (target 133–140 mmol/l)[181]. The required desmopressin dose might be somewhat higher than in non-pregnant patients, as the placental vasopressinase metabolizes any endogenous AVP. Caution is advisable in patients with impaired thirst sensation, as they may require a fixed daily fluid intake to avoid marked changes in plasma sodium concentration. After delivery, desmopressin can be stopped within days to weeks in patients with transient DI or reduced to the pre-pregnancy dose in those with permanent DI[15]. Desmopressin can be safely given during breastfeeding[182].

Quality of life

Formal assessment of QOL is limited to two studies in patients with central DI[183,184], although other QOL studies have included patients with DI who have traumatic brain injury and concurrent hypopituitarism[185]. Isolated and treated central DI is associated with a fairly normal QOL in both children[184] and adults[183], particularly when oral desmopressin is prescribed. Indeed, in patients with diminished QOL, the dose or timing of desmopressin treatment should probably be adjusted.

The Nagasaki Diabetes Insipidus Questionnaire, which consists of 12 questions, ten of which relate directly to central DI symptoms (liquid intake and urination, and limitations of daily life) and two to the effect of desmopressin and the patient's satisfaction with desmopressin, seems to provide a reliable measure of QOL in patients with central DI. Studies using this questionnaire revealed that concerns expressed by untreated patients about polyuria and heightened thirst in public settings consistently diminish when they receive nasal desmopressin, and when they are switched to an oral formulation[183]. Additional QOL benefits were reported in a subset of patients who lost weight when switched to oral desmopressin, presumably because of reduced polydipsia-induced weight gain[186]. Although some patients noted the inconvenience of not being able to eat with oral desmopressin, it did not lead to resumption of nasal treatment. Conversely, patients who were satisfied with nasal desmopressin showed no further benefit from switching to oral desmopressin.

The salutary effect of desmopressin on nocturia and incontinence in some patients with CWD, dipsogenic DI or partial central DI probably improves their QOL[187], as does the reported ability of clozapine to allow psychotic patients with PIP to be discharged from long-term inpatient facilities[177].

Outlook

Owing to their rarity, DI and primary polydipsia are fairly neglected disorders, in terms of both their inclusion in the medical education curriculum and research efforts to improve diagnosis and treatment. The prevalence of CWD is increasing in the general population[14]; which might be prevented or limited by greater awareness of the tendency of some individuals to take extreme measures when worried about their physical health.

Although many of the underlying mechanisms leading to acquired or hereditary DI or primary polydipsia are known, idiopathic forms of AVP deficiency are a large pathogenetic category in central DI, which in most cases results from autoimmune destruction of the neurohypophysis, and better classification and evaluation of these patients is needed. Furthermore, the increasing use of immune checkpoint blockade in patients with cancer has led to increasing incidence of hypophysitis

with mainly secondary adrenal insufficiency, secondary hypothyroidism and secondary hypogonadism[188], whereas only a few cases of posterior pituitary gland involvement have been reported[189]. The expected further increase in the use of immune checkpoint inhibitors in the coming years will need to be monitored.

In hereditary central DI, the genes responsible for autosomal recessive FNDI type b, autosomal recessive FNDI type d and X-linked recessive FNDI have yet to be identified[57]. Furthermore, in hereditary nephrogenic DI, questions remain about mechanisms of apparent AVPR2-dependent but cAMP-independent AQP2 trafficking, and the role of non-vasopressin modulators of AQP2 trafficking, such as prostaglandin E2, nitric oxide and adenosine.

Primary polydipsia undoubtedly encompasses a number of distinct disorders arising from learned behaviours, which induce anticipatory drinking or states of heightened arousal that are ameliorated by non-regulatory water drinking. Technological advances have enabled dissection of the components of motivational and affective influences on the homeostatic systems in the anterior hypothalamus, which regulate drinking behaviour and AVP secretion. We expect that the pathophysiology of these disorders and their relationship to one another and to other homeostatic and non-homeostatic behaviours will be revealed in the coming years.

For decades, the differential diagnosis of polyuria–polydipsia syndrome has been based on the indirect water deprivation test. In 2018, hypertonic saline infusion with copeptin measurement emerged as a new test with higher diagnostic accuracy, and was proposed as the new gold standard[102]. However, alternative tests should be explored because adverse effects of this test are quite common and constant surveillance and close monitoring is needed during the test to prevent a marked increase in serum sodium levels. A promising alternative is arginine infusion (followed by serum copeptin measurement), as it stimulates the release of various hormones, such as growth hormone and prolactin, from the anterior pituitary gland[190,191] and is a standard test to evaluate suspected growth hormone deficiency in children and adults. Arginine also stimulates the posterior pituitary gland, with a consequent increase in copeptin levels (M.C.-C., unpublished data), and the test differentiates between central DI and primary polydipsia with high diagnostic accuracy[192]. Further advantages include a possible lower risk of adverse effects of infusion compared with 3% saline infusion and practicality, even outside the hospital setting.

Finally, whereas central DI treatment is usually straightforward, treatment of nephrogenic DI is challenging. Novel treatments include non-peptide AVPR2 agonists or antagonists that act as molecular chaperones to rescue misfolded AVPR2 receptors (reviewed elsewhere[3]). Potential mechanism-based therapies for nephrogenic DI caused by *AVPR2* mutations include pharmacological chaperones to partially correct cellular misprocessing of mutant AVPR2 (REF.[193]), and drugs to bypass AVPR2, including prostaglandin receptor inhibitors, β3 adrenoreceptor agonists, secretin receptor agonists, cGMP phosphodiesterase inhibitors and others[194–197]. Mechanism-based therapy of nephrogenic DI caused by *AQP2* mutations is challenging because AQP2-mediated water permeability is required for physiological function of collecting ducts and thus cannot be bypassed. Chemical and molecular chaperones have been proposed as potential therapeutic agents for recessive nephrogenic DI caused by mutations that impair cellular trafficking of AQP2 (REF.[198]).

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