Best Practice & Research Clinical Endocrinology & Metabolism 40 (2026) 102065

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Diagnosis and treatment of hypernatremia

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ARTICLE INFO

Keywords:
hypernatremia
vasopressin
sodium
AVP deficiency

Hypernatremia, defined as a plasma sodium concentration greater than 145 mmol/l, represents a deficit of water relative to sodium and is most commonly due to free water loss and/or inadequate free water intake, rather than sodium excess. The reported prevalence of hypernatremia varies depending on the clinical setting with retrospective analyses identifying a prevalence of 0.5–1 % in the community but up to 10 % in intensive care units. Patients with reduced cognition or consciousness have impaired access to free water making them particularly vulnerable to hypernatremia. Hypernatremia is associated with poorer outcomes including longer length of hospital stay, in-hospital mortality, and odds of discharge to hospice or nursing home. This review will describe the diagnosis and management of hypernatremia providing insight into physiological mechanisms underpinning salt and water homeostasis with particular focus on arginine vasopressin deficiency as an endocrine cause of hypernatremia.

Introduction

Plasma sodium concentration is the main determinant of plasma osmolality and as such, it is maintained within a narrow physiological range by hypothalamic osmoregulation. Hypernatremia is defined as a plasma sodium concentration greater than 145 mmol/l, often classified as mild (plasma sodium 145–150 mmol/l), moderate (plasma sodium 151–155 mmol/l) and severe (plasma sodium $>$ 155 mmol/l) [1]. The reported prevalence of hypernatremia varies depending on the clinical setting with retrospective analyses identifying a prevalence of 0.5–1 % in the community but up to 10 % in intensive care units [2,3]. Usually, excessive water losses alone do not result in hypernatremia as increased plasma osmolality stimulates hypothalamic osmoregulation: secretion of arginine vasopressin (AVP) and thirst [4] (Fig. 1). Hypernatremia occurs when water losses are inadequately replaced which is often the case when patients cannot access free water [5]. Consequently, the elderly, infants and young children, hospitalised patients and any patient with reduced consciousness or reduced cognition is at high risk of developing hypernatremia. Patients with hypernatremia invariably have dysfunctional salt and water homeostasis as a result of either impaired access to free water, impaired thirst response or impaired ability to concentrate urine. Inpatient hypernatremia is most often seen in old, frail, bed bound patients who have appropriate physiological AVP secretion to concentrate urine but inadequate thirst or access to water. Notably, nursing home residents exhibit a ten-fold higher prevalence of hypernatremia compared to community dwelling elderly patients due to cognitive and physical barriers impairing access to free water [6]. Elderly patients have a reduced thirst appreciation [7] and often

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https://doi.org/10.1016/j.beem.2025.102065

Available online 4 November 2025

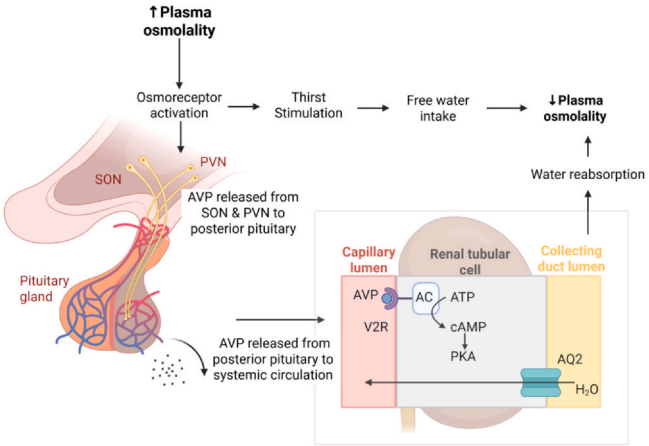

Fig. 1. Salt and water homeostasis. *Abbreviations: AC, Adenyl cyclase; ATP, Adenosine triphosphate; AVP, arginine vasopressin; AQ2, aquaporin 2; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; PVN, paraventricular nucleus; SON, supraoptic nucleus; V2R, vasopressin receptor type 2.*
(reproduced with permission from Tomkins et al. Best Pract. Res. Clin. Endocrinol. Metab. 2025) [4].

have iatrogenic precipitants of hypernatremia such as diuretic therapy or intentional fluid restriction in the setting of congestive cardiac failure [8]. Moreover, evidence suggests poor recognition and suboptimal management of hypernatremia in elderly patients resulting in increased morbidity and mortality [6,9,10]. Disorders of AVP, such as AVP deficiency or AVP resistance are rare.

Salt and water homeostasis

Under normal circumstances, hypothalamic osmoreceptors expressed in the subfornical organ (SFO) and the organum vasculosum of the lamina terminalus (OVLT) are activated in response to an elevation in plasma osmolality stimulating the synthesis and release of AVP. Additionally, in hypotensive states, AVP is released in response to stimulation of baroreceptors in the carotid sinus, aortic arch, cardiac atria and pulmonary venous system [11,12]. When plasma osmolality rises above ~285mosmol/kg (known as the osmotic threshold for AVP synthesis and secretion), specialized neurons of the SFO and OVLT depolarize and stimulate the synthesis of AVP in the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus. AVP is transported as a prohormone coupled with copeptin and neurophysin II, via neurosecretory granules to the posterior pituitary, where it is stored in nerve termini. Following osmoreceptor stimulation AVP is cleaved from it's prohormone and released into systemic circulation where it binds to vasopressin receptors including vasopressin 2 (V2) receptors on the basolateral membrane of renal collecting duct principal cells [4]. An intracellular cascade ensues, increasing intracellular cyclic adenosine monophosphate (cAMP) which promotes protein kinase A-mediated translocation of aquaporin 2 (AQ2) water channels from intracellular vesicles to the luminal membrane of the collecting duct. AQ2 water channels at the luminal membrane allow reabsorption of water from urine into blood along osmotic gradients. The SFO and OVLT also stimulate the thirst centre in the cerebral cortex at a slightly higher osmotic threshold than AVP, promoting free water intake [13]. The net result of urinary concentration and free water intake normalizes plasma osmolality and sodium concentration (Fig. 1). At plasma osmolalities below the osmotic thresholds both AVP release and thirst are inhibited, allowing hypotonic diuresis.

Acute vs. Chronic Hypernatremia, implications for treatment

Total body water (TBW) consists of two compartments, extracellular fluid (ECF) and intracellular fluid (ICF), and is estimated to be approximately 60 % of body weight in men and 50 % in women [14]. Normally, ECF and ICF account for 40 and 60 % of TBW, respectively [5]. Osmolalities in the ECF and ICF must be equal to allow free movement of water across cell membranes. When hypernatremia occurs, there is increased osmolality of the ECF compartment. To overcome the osmotic gradient between the ECF and ICF, water moves from the intracellular space resulting in cellular shrinkage and, at the level of the brain, reduced brain volume [15]. The brain undergoes adaptive processes to normalize brain volume involving rapid cellular uptake of inorganic ions (sodium, potassium and chloride) followed by a more delayed accumulation of organic osmolytes (myo-inositol, amino acids) [5]. Acute hypernatremia (< 48 h) is often accompanied with significant neurological symptoms (lethargy, weakness, seizures or even coma) due to these changes in brain volume and should be immediately corrected. Where the sodium trajectory is unknown or elevated for more than 48 h (chronic hypernatremia) osmotic brain adaptation has occurred, less symptoms are evident, and expert opinion favours a slower rate of correction of no more than 0.5 ml/l per hour and an maximal absolute change of 10 mmol/l per day [5]. Most of the evidence for slow correction in hypernatremia is founded in cases of paediatric hypernatremia [16–18]. The maximum safe rate of correction in adults has not been established. Reassuringly, there have been no reports of cerebral oedema due to rapid correction of hypernatremia in adults. In fact, a large retrospective analysis of 4265 patients identified longer hospital stay and higher mortality with slow correction of hypernatremia [19]. A reasonable approach, given the theoretical risk, is to aim for correction of

Table 1
Causes of hypernatremia [31–33].

Classification and Mechanism of Hypernatremia	Cause	Clinical features
Hypovolaemic hypernatremia Unreplaced free water and sodium loss	*Gastrointestinal losses:* Vomiting, diarrhoea, nasogastric drainage/suction, enterocutaneous fistula, lactulose *Renal losses:* Osmotic diuresis (glucose, mannitol or urea), loop/thiazide diuretics, post-obstructive diuresis, polyuric phase of ATN, intrinsic renal disease *Skin losses:* Insensible (fevers, burns), sensible (sweat) *Respiratory losses:* Excessive secretions or exhaled water vapor during hyperventilation	Hypotension Tachycardia Dry mucous membranes UOsm high UNa low
Dehydration Loss of free water due to reduced access to water or reduced thirst	*Water access/Thirst* Hypodipsia or inability to access free water	UOsm high, UNa variable
Euvolaemic hypernatremia Loss of free water	*AVP disorders* AVP-deficiency or resistance	Normal vital signs No signs of oedema AVP disorders: UOsm low, UNa variable
Hypervolaemic hypernatremia Gain of water and sodium	*Iatrogenic* Administration of relatively hypertonic fluid (3 % saline, sodium bicarbonate, hypertonic dialysate, sodium-containing medications, tube feeding)	Peripheral oedema UOsm high, UNa high

Abbreviations: ATN, acute tubular necrosis; AVP, arginine vasopressin; UNa, urinary sodium; UOsm, urine osmolality,

approximately 10 mmol/l per day, however, if this maximal target is inadvertently exceeded, plasma sodium does not need to be therapeutically raised again [20]. Results are awaited of a randomized clinical trial comparing the efficacy and safety of rapid intermittent bolus compared to slow infusion of electrolyte-free solution in management of severe hypernatremia [21].

Morbidity and mortality associated with hypernatremia

Mortality associated with hypernatremia varies from 20 % to 60 % depending on severity of hypernatremia, comorbidities and associated illnesses [3,15,22,23]. Hypernatremia is also associated with prolonged length of stay and increased perioperative morbidity including perioperative coronary events, pneumonia and venous thromboembolism [3,24]. In traumatic brain injury, severe hypernatremia confers an eight-fold increased risk of mortality [25], often heralding the onset of rising intracranial pressure, progressing to tonsillar herniation and death [26]. Delayed correction of hypernatremia, irrespective of severity of hypernatremia, results in increased in-hospital and 30-day mortality [19,27]. Despite this, there are numerous reports of suboptimal management and assessment of inpatient hypernatremia [9,27,28].

Diagnosis and treatment of hypernatremia

The underlying cause of hypernatremia is often evident from the clinical history (e.g. history of vomiting or diarrhoeal illness, neurosurgical intervention, traumatic brain injury and nursing home resident or cognitive impairment). Careful assessment of volume status guides the diagnosis and treatment of hypernatremia. Table 1 provides an outline of the causes of hypernatremia classified by volume status.

Hypovolaemic hypernatremia and dehydration

Hypovolaemic hypernatremia, is due to increased output from unreplaced losses (gastrointestinal, renal or skin sources). Hypovolaemia refers to loss of overall body fluid volume, both water and solutes including sodium. Hypernatremia ensues when water loss is greater than solute loss. Signs and symptoms of hypovolaemia include dry mucous membranes, abnormal skin turgor, delayed capillary refill time, reduced jugular venous pressure, tachycardia and hypotension (sometimes only evident on orthostatic measurement). Gastrointestinal losses may occur from vomiting or diarrhoea or from excessive nasogastric suction. Renal losses include osmotic diuresis due to glucose, urea or mannitol which increase urine output with losses of water in excess of sodium [29]. If losses are not adequately replaced hypernatremia ensues.

Dehydration, as opposed to hypovolaemia, occurs when there is net loss of water alone resulting in hypernatremia. Patients with mild dehydration may not present with hypotension or circulatory shock but will have subtle signs of volume depletion such as dry mucous membranes. Dehydration is often seen in patients with physical and cognitive barriers impacting on the ability to access water such as cognitive impairment, swallowing difficulties and poor mobility, commonly seen in nursing home residents and bed

bound patients. In this group, factors leading to a decline in neurological status precipitating reduced oral intake should be sought. A thorough clinical history and examination focusing on signs of concurrent infection, neurological event (stroke) or delirium should be performed. In one retrospective review of hypernatremic presentations to the emergency department, mean age was 79.9 years old with 55 % residing in medical institutions or requiring home care [27]. Most patients presented with dehydration in the setting of an infective illness. Under-correction of hypernatremia was associated with increased mortality and posed a significant issue in this cohort, with 68 % experiencing ongoing hypernatremia three days after admission [27].

Initial investigations include full blood count, urea, creatinine, sodium and electrolytes, glucose and urine osmolality. As infection is a common precipitant of hypernatremia [27], clinicians should have a low threshold to perform a septic screen alongside C-reactive protein, urine dipstick and chest X-ray. Pre-renal acute kidney injury may occur alongside hypernatremia and kidney function should be monitored carefully alongside sodium concentration during fluid resuscitation. Patients with diabetes may present with significant hypernatremia in the setting of hyperosmolar hyperglycaemic state (HHS) where, excessive osmotic diuresis due to hyperglycaemia results in dehydration and hypernatremia. Urgent management with intravenous fluids, intravenous insulin and careful electrolyte monitoring is required [30]. Urine osmolality is the definitive test to differentiate dehydration from an AVP disorder. If urine osmolality is greater than 700 mOsm/kg in the setting of hypernatremia, the urine is concentrated indicating adequate AVP secretion and the patient does not have an AVP disorder [31]. The most likely cause of hypernatremia in this case is dehydration. The major caveat to this rule is in the setting of hypotension or vasopressor use, baroregulated AVP release may lead to urinary concentration. Urine osmolality less than 300 mOsm/kg in the setting of hypernatremia should raise the suspicion for an AVP disorder [31].

Management of hypovolaemic hypernatremia and dehydration requires treatment of the precipitating factor (diarrhoea, vomiting, intercurrent illness/infection) and careful fluid resuscitation replacing the free water deficit and ongoing losses. Free water deficit can be calculated with the following equation:

Volume (L) = (Total body water) x weight in kg x [(sodium-140)/140] [5]

where total body water is 0.45 for women > 65 years, 0.5 for women < 65 years and for men > 65 years and 0.6 for men < 65 years [5]. This formula provides an estimate of the water deficit but can underestimate the deficit in patients with hypotonic fluid loss and in those with ongoing water losses [5]. Oral or enteral free water should be used whenever possible. It is important to consider the tonicity of fluid losses in hypovolaemic hypernatremia as inadvertent replacement of hypotonic losses with isotonic solution will further exacerbate hypernatremia [32]. When intravenous fluids are required hypotonic solutions, such as 5 % dextrose or 0.45 % sodium chloride, should be used. However, if the patient is presenting in hypovolaemic shock with hypotension, isotonic solution may be required for adequate resuscitation [8]. The sodium content of commonly used intravenous fluids is listed in Table 2. Monitoring of urine output and stool output alongside estimation of insensible losses is recommended to guide replacement of ongoing losses. Additional consideration should be given to patients with diabetes where dextrose solutions may result in hyperglycaemia, alternating with 0.45 % saline or oral/nasogastric water may be more appropriate. A cautious approach should be considered in patients at risk of volume overload (e.g. congestive cardiac failure). A thorough medication review is essential as numerous medications (e.g. diuretics, osmotic laxatives, parenteral feeds) may induce or exacerbate hypernatremia. Moreover, nephrotoxins should be held, if possible, due to risk of concurrent acute kidney injury. During treatment, clinical response, volume status, plasma sodium and electrolytes should be monitored regularly (at least every 12 h, and more frequently in the initial stages) and fluid resuscitation should be adjusted as appropriate. It is important to highlight a rational approach to patients approaching end-of-life where, hypernatremia is an expected abnormality and aggressive management is potentially inappropriate [8]. An approach to the initial assessment and management of hypovolaemic hyponatremia and dehydration is summarised in Fig. 2.

Hypervolaemic hypernatremia

Hypervolaemic hypernatremia is less common, usually iatrogenic in nature, and results in an increase in sodium that is in excess of a concomitant increase in total body water. Patients will have signs of volume overload such as peripheral oedema, raised jugular venous pressure and in some cases hypertension [15]. In the paediatric setting sodium overload from use of concentrated infant formula preparations has been described [24]. In adults, most cases of hypervolaemic hypernatremia are related to iatrogenic administration of relatively hypertonic fluid [32]. Diuresis alongside free water replacement (with oral water or 5 % dextrose) is recommended to resolve sodium excess whilst also resolving hypertonicity. Diuretics in isolation will induce more aquaresis relative to natriuresis exacerbating hypertonicity and hypernatremia [15]. Sodium administration should be minimised, especially in the context of critical care where patients may be administered medications in 0.9 % saline [33].

Table 2
Sodium content of intravenous fluids.

Intravenous fluid	**Sodium concentration** mmol/l
5 % dextrose in water	0
0.45 % sodium chloride in water	77
Ringer's lactate/Hartmann's solution	130
0.9 % sodium chloride in water	154

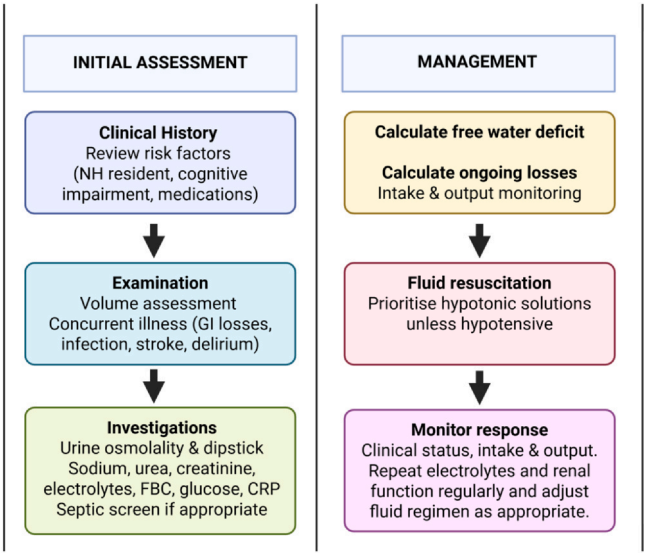

Fig. 2. Approach to the management of hypovolaemic hypernatremia in the general medical patient [5,8]. Abbreviations: NH, nursing home; GI, gastrointestinal; FBC, full blood count; CRP, C-reactive protein.
Created in BioRender. Tomkins, M. (2025) https://BioRender.com/snz4rzh.

Euvolaemic hypernatremia

Most cases of euvolaemic hypernatremia will be due to a disorder in AVP, AVP-deficiency (AVP-D, previously called central diabetes insipidus) or AVP resistance (AVP-R, previously called nephrogenic diabetes insipidus). Patients with AVP disorders present with polyuria and polydipsia due to lack of urine concentrating capacity from either a defect in AVP synthesis in the hypothalamus and release from the posterior pituitary (AVP-D) or resistance to AVP at the level of the kidney (AVP-R). The major causes of AVP-D and AVP-R are summarised in Table 3. In the setting of AVP disorders, excess renal loss of water results in elevated plasma osmolality which stimulates the thirst response. As such, patients with AVP disorders present with high-normal plasma sodium concentration accompanied with polydipsia and do not commonly encounter significant hypernatremia unless there is a diminished thirst response, lack of access to water or concomitant illness [34]. AVP disorders should be distinguished from primary polydipsia (PP) where compulsive excessive drinking lowers the plasma osmolality below the osmotic threshold for AVP secretion resulting in polyuria [31]. Patients with PP rarely experience hypernatremia and more often have normal or mildly low plasma sodium concentrations [31], discussion of PP is beyond the scope and context of this review. [35]

Initial laboratory investigations should include renal function and serum electrolytes with particular focus on sodium, calcium and potassium concentrations. Plasma and urinary glucose should be measured in any patient presenting with polyuria and polydipsia to investigate the presence of diabetes mellitus. Quantification of urine output to confirm polyuria (urine output exceeding 50 ml/kg per day or as total daily urine volume > 3 litres) should be performed. Urine osmolality, as a biomarker of AVP secretion, is the most useful initial test to determine renal concentrating ability. If urine osmolality is greater than 700 mOsm/kg in the setting of hypernatremia there is adequate physiologically appropriate AVP secretion and the patient does not have an AVP disorder [31]. The major caveat to this rule is in the setting of hypotension or vasopressor use, baroregulated AVP release may lead to urinary concentration. Urine osmolality less than 300 mOsm/kg in this clinical context should raise the suspicion for an AVP disorder [31].

For decades, the water deprivation test (WDT), an indirect test of AVP action, was the standard diagnostic test for the evaluation of polyuria and polydipsia. It involves two key steps, an initial period of water restriction (usually for 8 h) and, if required, this is followed by administration of desmopressin (dDAVP) to differentiate between AVP-D and AVP-R. Upon dehydration, rising plasma sodium and osmolality should stimulate AVP secretion which should increase urine osmolality (> 700 mOsm/kg) when AVP secretion and action are intact. Patients with AVP disorders fail to concentrate urine during this phase. Upon administering dDAVP, patients with AVP-deficiency will exhibit a rise in urine osmolality where urine in AVP-resistance remains dilute. Authors differ on the threshold for normal response to dDAVP with urine osmolality > 700–800 mOsm/kg or a doubling of baseline accepted [36,37]. However, it should be noted that prolonged significant polyuria of any cause may reduce renal concentrating capacity thereby reducing the diagnostic accuracy of the test [38]. Moreover, patients with partial AVP-D may have residual AVP secretion and concentrate urine [39]. In addition, the WDT is cumbersome and unpleasant for patients. It carries the risk of inducing hypernatremia and severe dehydration and is potentially dangerous in patients with complete AVP-D [31]. If a patient is hypernatremic, measurement of urine osmolality alone should be sufficient to confirm the diagnosis of AVP deficiency or resistance and it is neither clinically appropriate or safe to deprive the patient of water. The diagnostic challenge in the setting of euvolaemic hypernatremia with low urine osmolality is distinguishing AVP-D from AVP-R. Measurement of AVP would be helpful with low concentration expected in AVP-D and high concentrations in AVP-R. Direct measurement of AVP is possible, however, there are significant

Table 3
Causes of AVP disorders [31,82].

AVP-Deficiency	
Familial	
DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness) syndrome	
Acquired	
Iatrogenic	Surgery for pituitary adenoma and sella/suprasellar lesions
Neoplastic	Craniopharyngioma
	Germinoma
	Pinealoma, glioma, meningioma
	Pituitary stalk metastases (breast, lung)
	Lymphoma, leukemia
Traumatic	Traumatic brain injury
Vascular	Subarachnoid haemorrhage
	Intracranial haemorrhage
	Sheehan's syndrome
Inflammation/Infection	Sarcoid
	Histiocytosis
	Granulomatosis with polyangiitis
	Post-tuberculous meningitis, post encephalitis, toxoplasmosis, abscess
	HIV
	COVID − 19 infection
	Systemic lupus erythematosus
Autoimmune	Lymphocytic infundibulo-neurohypophysitis
Pregnancy	Due to vasopressinase enzyme
CNS malformation	Septo-optic dysplasia
	Agenesis of corpus callosum
	Empty sella syndrome
	Pituitary hypoplasia
Idiopathic	
AVP-Resistance	
Familial	
Vasopressin V2 receptor (AVPR2) gene mutations (X-linked)	
Aquaporin − 2 (AQP2) gene mutation (autosomal dominant or recessive)	
Acquired	
Medications	Lithium, Cisplatin, Amphotericin B, Demeclocycline, Aminoglycosides, Dopamine, Orlistat
Electrolyte disturbances	Hypercalcaemia (persistently above 2.75 mmol/l)
	Hypokalaemia (persistent severe hypokalaemia)
Vascular	Sickle cell disease or trait
Infiltrative	Amyloidosis, Sarcoidosis
	Sjogrens syndrome
Mechanical	Polycystic kidney disease
	Urethral obstruction

preanalytical and methodological limitations of the AVP assay making it an impractical diagnostic test [31]. A suitable alternative is plasma copeptin. Copeptin is the biologically inert C-terminal locus, enzymatically cleaved from preprovasopressin and cosecreted from the posterior pituitary in equimolar amounts with AVP and is easily measured in plasma or serum with a sandwich immunoassay [40]. Patients with AVP-R have elevated baseline copeptin > 21.4pmol/l, easily distinguishing AVP-R from AVP-D where copeptin levels remain low [41]. Low plasma copeptin (< 2.5pmol/l) has also proved useful to predict AVP-D post-pituitary surgery [42]. The greatest diagnostic challenge in patients with polyuria and polydipsia is distinguishing between AVP-D and primary polydipsia where plasma copeptin is both accurate and convenient [41,43-46].

If the patient is acutely unwell and not suitable for water deprivation test or hypertonic saline infusion, as is often the case with hypernatremia post neurosurgical intervention or traumatic brain injury, the modified Seckl and Dunger criteria, initially suggested for diagnosis of AVP-D following pituitary surgery may be employed [47]. After exclusion of hyperglycaemia or mannitol therapy these criteria include:

1. Polyuria defined as urine volume > 2 ml/kg/hr or > 300 ml in two consecutive hours
2. Hypotonic urine defined as urine osmolality < 300 mOsm/kg
3. Increased plasma osmolality > 300 mOsm /kg. In the acute phase, plasma sodium is more reliable, with plasma sodium > 145 mmol/l alongside polyuria suggestive of AVP-D.

AVP deficiency

AVP-D is rare with estimated frequency of 1 case per 25,000 of the population [44]. AVP-D develops as a result of three possible mechanisms: anatomical destruction, traumatic damage or autoimmune destruction of AVP-secreting neurons [31]. Additionally, familial, usually monogenic, forms of AVP-D caused by mutations of the AVP gene occur which present in childhood [48–50]. A high

index of suspicion for AVP-D is required in patients presenting with polyuria and/or hypernatremia post-neurosurgical intervention for pituitary masses, post subarachnoid haemorrhage or post-traumatic brain injury (TBI), conditions with reported incidence of AVP-D 18 %, 15 % and 20 %, respectively [51–53]. In a series of 881 patients, 18 % experienced immediate postoperative AVP-D following transsphenoidal surgery, which persisted in only 2 % of cases. Factors associated with development of permanent AVP-D were intraoperative cerebrospinal fluid leak, craniopharyngioma or Rathke's cleft cyst. Cushing's disease was associated with greater risk of transient (22.2 %) but not permanent AVP-D [51]. Longitudinal analysis of survivors of TBI demonstrates a transient course of AVP-D with median duration of 4 days [26] and recovery within 10 days in the majority of cases [54].

The majority of patients with AVP-D have intact thirst [55], however, a rare disorder of concomitant AVP-D and absent or diminished thirst response, adipsic AVP-D, carries high morbidity and significant risk of dysnatremia [34]. Adipsic AVP-D has been reported in a number of conditions including patients who have undergone neurosurgical clipping of anterior communicating artery (ACOM) aneurysms following subarachnoid haemorrhage [56]. Perforating branches of the ACOM provide the vascular supply to the osmoreceptors responsible for both thirst appreciation and AVP release in the anterior hypothalamus hence, clipping of the ACOM can cause necrosis of the anterior hypothalamus with subsequent loss of AVP stimulation and thirst appreciation. Adipsic AVP-D may also occur as a result of destruction of the hypothalamus from a lesion or treatment (surgery) which compromises the osmoreceptors [57,58]. Loss of thirst is usually permanent although occasional cases of thirst recovery have been described [59]. Thankfully, newer approaches to the treatment of craniopharyngiomas have reduced the risk of adipsic AVP-D.

AVP has a short plasma half-life of 5–10 min, making it unsuitable for therapeutic use in the management of AVP-deficiency. The synthetic analog desmopressin [dDAVP (deamino D-arginine vasopressin)] has been modified by the removal of the amino group of the cysteine amino acid to prolong half-life from 5 min to 6–8 h and reduce vasoconstrictor (V1 receptor) effects [31]. This permits dDAVP administration twice or 3 times daily. dDAVP is available in oral, nasal and parenteral forms. Oral desmopressin is favoured due to the ease of administration, sustained efficacy, and patient preference [34]. Peak clinical effect occurs within 2 h of ingestion, coinciding with maximal plasma concentrations, and the antidiuretic action persists for 6–12 h [60]. The duration of action and the magnitude of antidiuresis is directly related to the dose of dDAVP [61]. Intranasal desmopressin can be administered as either metered-dose spray or via rhinyl tube. The duration of antidiuretic effect is more variable than oral preparations, ranging from 5 to 21 h [62] and efficacy may be compromised not only by the patient's skill but local factors such as nasal mucosal inflammation, congestion or scarring. Nasal preparations are not always suitable following transsphenoidal surgery when nasal packing is required [31]. dDAVP can also be administered via the intravenous or subcutaneous route, useful in the perioperative setting and in the management of transient AVP-deficiency after traumatic brain injury or transsphenoidal surgery [31]. Following an intravenous dose of 1 μg, the peak antidiuretic effect is observed within 12 h. Higher doses (up to 8 μg) can prolong the duration of action up to 48 h [63]. Hyponatremia remains the side effect of most clinical concern [31].

Acute AVP deficiency is commonly observed following transsphenoidal surgery for pituitary or suprasellar tumours, TBI, and subarachnoid haemorrhage [26,64]. It typically presents with the sudden onset of polyuria within 1–2 days of surgery or a traumatic insult. Treatment of acute AVP deficiency aims to reduce inappropriate renal losses by administering dDAVP and to replace the free water deficit. Patients should be instructed to drink to thirst. If physical or cognitive impairment precludes this, hypotonic intravenous fluids can be administered to normalise serum sodium. Acute AVP deficiency is treated with dDAVP, administered subcutaneously or intramuscularly. Dose of dDAVP varies depending on the duration of action required, ranging from 0.5 μg to 2 μg. Our practice is to give 1 μg subcutaneously. Many patients only require a single dose of dDAVP as AVP deficiency is usually transient [65]. Further parenteral doses are only required if hypotonic polyuria recurs (urine output $>$ 300 ml/h for two hours, urine osmolality $<$ 300 mOsm/kg) [66]. A survey found a strong consensus among pituitary endocrinologists for administering dDAVP on a PRN basis as opposed to regular doses in the immediate post-operative period [67].

Rarely, a triphasic response can occur. This response is characterised by transient acute AVP deficiency, followed by hyponatremia due to the syndrome of inappropriate antidiuresis (SIAD) and finally permanent AVP deficiency [68]. AVP deficiency may coexist with anterior hypopituitarism, including ACTH deficiency. ACTH deficiency can mask AVP deficiency, as cortisol is required for free water excretion. Consequently, treatment of ACTH deficiency with hydrocortisone can unmask AVP deficiency, leading to the sudden onset of polyuria.

In patients with persistent polyuria, beyond 72 h, a low dose of regular oral dDAVP can be initiated and titrated as appropriate. Persistent AVP deficiency following TBI may indicate raised intracerebral pressure. In patients with TBI, this is a particularly poor prognostic indicator which is associated with a high mortality [26]. If dDAVP is continued on hospital discharge, patients should be informed about the potential risk of the triphasic response and the need for to have their plasma sodium measured if they develop symptoms suggestive of hyponatremia, such as headache and nausea [36]. Posterior pituitary function should be retested after 3–6 months to assess for resolution of AVP deficiency [69].

Management of chronic AVP deficiency focuses on providing symptomatic relief by reducing polyuria and polydipsia. A single nocturnal dose of dDAVP is often sufficient to control nocturia and allow an unbroken sleep in patients with partial AVP deficiency. It also allows a daytime aquaresis which reduces the risk of developing hyponatremia. Patients with intact osmoreceptor-mediated thirst can compensate for polyuria by increasing fluid intake. As a result, hypernatremia in ambulatory patients with AVP deficiency is uncommon in the outpatient setting with a reported prevalence of 1.4 % [34]. In cases of complete AVP deficiency, two to three daily doses of dDAVP are typically required. The main risk of dDAVP administration is hyponatremia as dDAVP restricts free water excretion from the kidneys, irrespective of plasma osmolality, excessive fluid intake can lead to a dilutional hyponatremia [34]. A retrospective review of 147 outpatients with AVP deficiency reported that 41 % were hyponatremic on at least one occasion. Mild hyponatremia (plasma sodium 131–134 mmol/L) occurred in 27 % of patients, while more significant hyponatremia (plasma sodium $\leq$130 mmol/L) was observed in 15 % [34]. The harmful effects of mild chronic hyponatremia are increasingly recognised, including

gait disturbances, increased falls risk, osteoporosis and higher mortality [70–74]. More severe acute hyponatremia can cause seizures, coma or death due to cerebral oedema. Several strategies are employed in clinical practice to prevent the development of hyponatremia in patients receiving dDAVP:

1. Delaying a dose of dDAVP once per week until an aquaresis has developed (at least three large volume urinations), after which point the patient can take their medication.
2. Omit one dose of dDAVP per week. Although this is an effective method to prevent hyponatremia, the resulting polyuria can significantly interfere with patient's daily activities.

The results of a recent large-scale patient survey supported the effectiveness of the above strategies [75]. Hyponatremia occurred in 17 % of patients consistently employing these strategies, compared to 32 % in those unaware of these strategies and 26 % who were aware but used alternative approaches [75].

Patients with AVP deficiency are at risk of hypovolaemic hypernatremia with conditions such as vomiting or diarrheal illnesses, which compromise not only the ability to take oral fluids, but also the capacity to retain oral desmopressin. Patients should be educated to seek early medical advice during gastroenteritis or protracted vomiting.

Dysnatremia commonly arises in hospitalised patients with AVP deficiency. Rates of hyponatremia of up to 74 % have been reported, primarily attributable to the over-zealous use of hypotonic intravenous fluids. Hypernatremia affects 20 % of inpatients with AVP-D due to hypovolaemia (GI illness) and dehydration (fasting, restricted access to fluids or dDAVP) [34]. Medication errors, missed or delayed doses of dDAVP, and poor healthcare professional awareness of the critical importance of dDAVP frequently result in poor outcomes, including mortality, in patients with AVP-D [75–78]. The Society of Endocrinology developed evidence-based guidelines for the inpatient management of AVP deficiency [78,79] recommending all hospitalised patients with AVP deficiency are referred to the endocrinology team to oversee dDAVP prescribing and fluid and electrolyte balance. It also recommends designating dDAVP as an alert medication to ensure 24-hour availability. The new nomenclature "arginine vasopressin deficiency (AVP-D)" for central diabetes insipidus, and "arginine vasopressin resistance (AVP-R)" for nephrogenic diabetes insipidus [80] aims to better reflect the underlying pathophysiology of diabetes insipidus, as well as avoid any confusion between diabetes insipidus and diabetes mellitus.

Appropriate management during periods of fasting consists of parenteral dDAVP and intravenous isotonic fluids, with close monitoring of urine output and electrolyte levels throughout [66]. Management principles for patients who develop hypernatremia include limiting water losses by administering dDAVP and correcting water deficits with either free water or hypotonic fluids. Cases of mild hypernatremia (plasma sodium 145–148 mmol/L) can be managed by ensuring access to and promoting adequate oral intake. In patients with physical or cognitive impairment, gentle rehydration with isotonic intravenous fluids (0.9 % NaCl) can normalise the serum sodium. In cases of more severe hypernatremia (plasma sodium > 149 mmol/L), hypotonic fluids including free water (via a nasogastric tube), or intravenous 5 % dextrose or 0.45 % saline are required. Hypernatremia is also associated with an elevated haematocrit and hypercoagulable state, which significantly increases the risk of venous thromboembolism. This is particularly critical in patients with adipsic AVP deficiency, where fatal pulmonary embolism has been reported [58]. Given these risks, a low threshold for prescribing low-molecular-weight heparin is recommended for this patient cohort.

AVP resistance

AVP-R can be inherited or acquired. Inherited forms, due to gene mutations of the V2 receptor, present in childhood, where AVP-R in adulthood is usually acquired [15]. A myriad of medications, in particular lithium and antibiotics, have been implicated in acquired AVP-R [81]. Causes of AVP-R are summarised in Table 1. In most cases, AVP-R is reversible upon discontinuation of the offending medication, however, lithium therapy causes chronic tubulointerstitial scarring and chronic kidney disease resulting in persistent AVP-R [15]. Management of AVP-R is challenging and patients do not respond well to desmopressin. The main treatment goal is to ensure adequate replacement of fluid losses. Thiazide diuretics, amiloride, a low-sodium diet and non-steroidal anti-inflammatory drugs are useful in reducing polyuria and polydipsia however carry a risk of nephrotoxicity [38]. Close monitoring of sodium concentration and renal function is required.

Conclusion

Hypernatremia is associated with poor clinical outcomes, including mortality, and requires a thorough clinical approach to ascertain the underlying cause, chronicity and volume status which ultimately guide the diagnosis and treatment. Restoration of plasma sodium with appropriate monitoring of clinical status, urine output and electrolyte concentration is required. Healthcare professionals should be aware of the risks of medication error and omission in patients with AVP deficiency and this group of vulnerable patients should have expert endocrinology input when hospitalized.

Research Agenda

- Establishing the safe and effective correction rate of hypernatremia in adults is a major knowledge gap. To date, there are no convincing cases of poor neurological outcome due to fast correction and there is emerging evidence that slow correction may be linked to poorer outcomes.
- Early recognition of AVP-D following neurosurgical intervention, traumatic brain injury or subarachnoid haemorrhage would prevent unnecessary cases of hypernatremia which is associated with poorer outcomes, including mortality. The use of plasma copeptin in these cases is promising and is an area of further research focus.
- Healthcare professional awareness and understanding of AVP-D is poor, with many patients reporting suboptimal care during periods of hospitalization. Advances have been made with specific guidance from the Society for Endocrinology and changing the nomenclature from diabetes insipidus. Ongoing work in this area will further improve this knowledge gap.
- Patients with adipsic AVP-D are particularly at risk of dysnatremia due to complete loss of hypothalamic stimuli for osmoregulation (both AVP and thirst appreciation are impaired). The utility of point-of-care testing in the community for these patients is yet to be explored and may be beneficial in this group of vulnerable patients.

Practice Points

- Hypernatremia represents a deficit of water relative to sodium and is most commonly due to free water loss and/or inadequate free water intake, rather than sodium excess.
- Nursing home residents and elderly patients are particularly at risk of hypernatremia due to physical and cognitive barriers impairing free water access.
- Urine osmolality is a useful biomarker of AVP secretion.
- Treatment goals of hypernatremia include treating the underlying cause, replacing free water losses and avoiding exacerbation of hypertonicity. Patients require careful monitoring of clinical status, plasma sodium and urine output aiming for maximal correction of 10 mmol/l per day.
- Patients with AVP-deficiency are particularly vulnerable to dysnatremia when hospitalised and expert care with endocrinology input is recommended. Any patient with AVP-D who is required to fast should have a prospective plan in place, minimizing fasting, with appropriate dDAVP, isotonic fluids and electrolyte monitoring during the perioperative period under the supervision of an endocrinologist.

Funding Acknowledgements

MT is an Irish Clinical Academic Training (ICAT) programme fellow, supported by the Wellcome Trust and the Health Research Board (Grant Number 203930/B/16/Z), the Health Service Executive, National Doctors Training and Planning, Republic of Ireland and the Health and Social Care, Research and Development Division, Northern Ireland.

Declaration of Competing Interest

The authors declare they do not have any conflicts of interest

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