Hyponatremia and antidiuresis syndrome

Hyponatrémie et syndrome d’antidiurèse

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Résumé

L’hormone anti-diurétique (HAD) ou arginine vasopressine (AVP) est principalement régulée par l’osmolalité plasmatique mais également par des stimuli non osmotiques dont la volémie et le stress. Des liens entre les métabolismes hydro-ionique et glucidique ont aussi récemment été mis en évidence. L’AVP agit par l’intermédiaire de récepteurs de trois types : V1a ou V1 exerçant des effets vaso-constricteurs, V1b ou V3 hypophysaires participant à la sécrétion de l’ACTH, V2 rénaux, réduisant l’excréption d’eau pure par leur couplage aux canaux hydriques (aquaporine 2). Le syndrome d’antidiurèse est une forme d’hyponatrémie hypoosmolair, euvolemique caractérisée par une clairance de l’eau libre négative avec osmolalité urinaire inappropriée et hyperhydratation intra-cellulaire, en l’absence d’insuffisance rénale, surrénale et thyroïdienne. Quatre-vingt-dix pour cent des syndromes d’antidiurèse s’associent à un hypervasopressinisme, tandis que, dans 10 % des cas, la vasopressine n’est pas détectable. C’est la raison pour laquelle le terme « syndrome d’antidiurèse » (SIAD) est plus adapté que la classique dénomination « syndrome de sécrétion inappropriée d’HAD » (SIADH). La symptomatologie clinique, la morbidité et la mortalité des hyponatrémies sont liées à leur profondeur, d’une part, à leur rapidité d’installation et à leur durée, d’autre part. Même dans les hyponatrémies modérées considérées comme asymptomaticques, le risque de chute est très accru en raison de troubles de la marche et de l’attention, mais aussi d’une rhabdomyolyse, majorant le risque fracturaire. Le diagnostic étiologique des hyponatrémies repose sur l’analyse de l’osmolalité plasmatique (OsmP) calculée ou mesurée, d’une part, de la volémie (pli cutané de déshydratation, œdèmes, d’autre part. L’hyperglycémie et l’hypertiglycéridémie entraînent une hyponatrémie respectivement hyper- et normo-osmolaires. Les pertes de sel d’origine digestive, rénale, cutanée ou parfois cérébrale sont des hyponatrémies hypoosmolaires hypopanolèmes (pli cutané), tandis que des œdèmes sont présents dans les hyponatrémies hypoosmolaires hypervolémiques de l’insuffisance cardiaque, du syndrome néphrotique et de la cirrhose. Certaines endocrinopathies (insuffisance en glucocorticoïde et hypothyroïdie) s’associent à une hyponatrémie hypoosmolair, normovolémique qui doit être distinguée des SIADH. Indépendamment de l’insuffisance cortico-surénale périphérique, l’hypoaldostéronisme isolé peut également s’accompagner d’un hypervasopressinisme secondaire à l’hypovolémie, qui répond à la prescription de minéralo-corticoïdes. Les causes des SIADH sont classiques : néoplasies (singulièrement le cancer bronchique à petites cellules), iatrogènes (particulièrement les psychotropes, la chimiothérapie), pulmonaires et cérébrales. Certaines causes ont été plus récemment décrites : hyponatrémies familiales par mutation activatrice du récepteur de la vasopressine 2, récessive liée à l’X; insuffisance corticotrope liée à une interférence médicamenteuse entre certains glucocorticoïdes inhalés et les inhibiteurs du cytochrome p450 tels que les anti-rétroviraux et l’itraconazole… Le SIADH des marathoniens expose à un risque d’encéphalopathie hypotonique avec œdème cérébral mortel. Sur le plan thérapeutique, le traitement du SIADH repose sur la restriction hydrique et la déméclocycline. Les antagonistes des récepteurs V2 ne sont pas encore commercialisés en France. Ces aquaretiques semblent efficaces sur le plan clinique et biologique, sans amélioration démontrée à ce jour de la mortalité dans les hyponatrémies normo- ou hypervolémiques. Il ne faut bien sûr pas omettre de traiter un déficit corticotrope même subtil, d’introduire de la fludrocortisone en cas d’hypoaldostéronisme isolé, d’interrompre les médicaments iatrogènes.

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Abstract

Antidiuretic hormone (ADH), or arginine vasopressin (AVP), is primarily regulated through plasma osmolarity, as well as non-osmotic stimuli including blood volume and stress. Links between water-electrolyte and carbohydrate metabolism have also been recently demonstrated. AVP acts via the intermediary of three types of receptors: V1a, or V1, which exerts vasoconstrictive effects; pituitary gland V1b, or V3, which participates in the secretion of ACTH; and renal V2, which reduces the excretion of pure water by combining with water channels (aquaporin 2). Antidiuresis syndrome is a form of euvoelaemic, hypoosmolar hyponatraemia, which is characterised by a negative free water clearance with inappropriate

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urine osmolality and intracellular hyper-hydration in the absence of renal, adrenal and thyroid insufficiency. Ninety percent of cases of antidiuresis syndrome occur in association with hypersecretion of vasopressin, while vasopressin is undetectable in 10% of cases. Thus the term “antiuresis syndrome” is more appropriate than the classic name “syndrome of inappropriate ADH secretion” (SIADH). The clinical symptoms, morbidity and mortality of hyponatraemia are related to its severity, as well as to the rapidity of its onset and duration. Even in cases of moderate hyponatraemia that are considered asymptomatic, there is a very high risk of falls due to gait and attention disorders, as well as rhabdomyolysis, which increases the fracture risk. The aetiological diagnosis of hyponatraemia is based on the analysis of calculated or measured plasma osmolality (POsm), as well as blood volume (skin tenting of dehydration, oedema). Hyperglycaemia and hypertriglyceridaemia lead to hyper- and normoosmolar hyponatraemia, respectively. Salt loss of gastrointestinal, renal, cutaneous and sometimes cerebral origin is hypovolaemic, hypooosmolar hyponatraemia (skin tenting), whereas oedema is present with hypervolaemic, hypooosmolar hyponatraemia of heart failure, nephrotic syndrome and cirrhosis. Some endocrinopathies (glucocorticoid deficiency and hypothyroidism) are associated with euvoalamic, hypooosmolar hyponatraemia, which must be distinguished from SIADH. Independent of adrenal insufficiency, isolated hypoaldosteronism can also be accompanied by hypersecretion of vasopressin secondary to hypovolaemia, which responds to mineralocorticoid administration. The causes of SIADH are classic: neoplastic (notably small-cell lung cancer), iatrogenic (particularly psychoactive drugs, chemotherapy), lung and cerebral. Some causes have been recently described: familial hyponatraemia via X-linked recessive disease caused by an activating mutation of the vasopressin 2 receptor; and corticotropin insufficiency related to drug interference between some inhaled glucocorticoids and cytochrome p450 inhibitors, such as the antiretroviral drugs and itraconazole, etc. SIADH in marathon runners exposes them to a risk of hypotonic encephalopathy with fatal cerebral oedema. SIADH treatment is based on water restriction and demeclocycline. V2 receptor antagonists are still not marketed in France. These aquaretics seem effective clinically and biologically, without demonstrated improvement to date of mortality in eu- and hypervolaemic hyponatraemia. Obviously treatment of a corticotropic deficit, even subtle, should not be overlooked, as well as the introduction of fludrocortisone in isolated hypoaldosteronism and discontinuation of iatrogenic drugs.

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1. Introduction

Hyponatraemia, defined as a serum sodium concentration below 135 mmol/L, is the most common electrolyte anomaly in hospitalised patients, contributing to an increase in morbidity and mortality. The syndrome of inappropriate antidiuretic hormone secretion, or SIADH, is the most frequent cause of hyponatraemia in these patients [1].

SIADH was described by Schwartz and Bartter in 1957 in two patients with lung cancer who presented with hyponatraemia without hypovolaemia, a urine concentration disorder and sodium loss [2]. SIADH, which was identified before the discovery of the antidiuretic hormone (ADH, also known as vasopressin or AVP), should rather be called “antiuresis syndrome”. Indeed, it is sometimes related to causes other than ADH secretion that is inappropriate to plasma osmolarity, as shown in the studies of Zerbe and Robertson [3]. They documented four types of vasopressin secretion in SIADH:

- erratic fluctuations (37% of cases);
- resetting of the osmostat (33% of cases);
- constant secretion of AVP (16% of cases), and;
- the syndrome of inappropriate antidiuresis (SIAD), in which the level of vasopressin was undetectable (14% of cases).

This SIAD was related to:

- possible renal tubular hypersensitivity, for example, linked to excess activity of aquaporin or prostaglandins;
- secretion of vasopressin-like peptide, such as oxytocin or neurophysins, or;
- secretion of a natriuretic hormone;
- situations that have all been reported since then.

Recent advances in the knowledge of these water-electrolyte and endocrine disorders have been made, notably in the field of epidemiological studies, pathogenic consequences and therapeutic choices, which justify this update report.

2. Prevalence of hyponatraemia

The prevalence of hyponatraemia varies according to the populations studied.

2.1. Elderly persons in good health

Hyponatraemia is found in 4% of elderly persons in good health [4], whereas serum sodium concentrations inferior to 137 mmol/L have been noted in 11% of them [5].

2.2. Hospitalised persons

Hyponatraemia occurred in 8% of patients from a cohort of close to 8000 patients hospitalised for pneumonia [6], while 56% of patients hospitalised for cerebral haemorrhage presented hyponatraemia, 20% of which were below 125 mmol/L [7].

Therefore, 15 to 20% of hospitalised patients present serum sodium concentrations below 135 mmol/L upon their admission, 3 to 6% present below 130 mmol/L, and 1 to 3% below 125 mmol/L. Over 50% of these patients present with SIADH criteria.

3. Prognosis

The prognosis of hyponatraemia depends on its severity, its cause and the quality of its therapeutic management. It can be...
assessed in the short- or long-term. The rapidity at which the hyponatraemia occurred is a contributing factor of decreased clinical tolerance.

3.1. Short-term prognostic factors

3.1.1. Severity of hyponatraemia

There is a 26% mortality of hospitalised patients presenting with serum sodium levels less than 125 mmol/L, and that of patients with serum sodium below 115 mmol/L is around 50%. These figures are significantly higher than those of patients with normal sodium levels, which are around 9% [8].

3.1.2. Cause of hyponatraemia

3.1.2.1. Heart failure. A first study on a relatively limited number of heart failure patients [9] did not find a relationship between hyponatraemia and mortality in patients receiving maximum treatment. However, a subsequent study on over 8000 patients enabled a predictive mortality score to be calculated. Varying from 1 to 3, it took into account hypoalbuminaemia, hyponatraemia and hyperazotaemia, and found that the risk of mortality varied from 1 to 20% at 30 days, and from 11 to 56% at one year [10].

3.1.2.2. Liver diseases. Hyponatraemia is also a factor of early mortality in alcoholic hepatitis with ascites and in cirrhosis. It enters into the calculation of the modified MELD score (MELD Na) in alcoholic hepatitis, and is an independent prognostic factor of the MELD score in cirrhosis [11,12].

3.1.2.3. Kidney failure. Hyponatraemia that occurs in predialysis patients with kidney failure is associated with increased mortality [13].

3.1.3. Nature of the treatment

Without treatment, mortality is 37%, whereas it is 13% if a specific hyponatraemia treatment is initiated [14].

3.2. Long-term prognosis

The outcome of patients presenting with hyponatraemia during hospitalisation was also assessed at 1 year and 5 years: the mortality was 14.5% in patients with serum sodium less than 135 mmol/L on admission in a series of 100,000 patients that were evaluated between 2000 and 2003 [15].

It has therefore been well demonstrated that hyponatraemia is associated with higher mortality than in its absence, worsening the prognosis relative to the disease itself. It is however difficult to ascertain to what degree the hyponatraemia is a reflection of the severity of the underlying disease.

4. Pathophysiology of SIADH

4.1. Nature of ADH

ADH is a peptide of nine amino acids, in which two cysteine residues are bound by a disulfide bridge. An arginine residue distinguishes it from the vasopressin of other mammals.

4.2. Origin

Vasopressin is synthesised in the hypothalamic supraoptic and paraventricular nuclei. It migrates in the form of clusters along the neuronal axons through the pituitary stalk to the neurohypophysis, where it is secreted according to osmotic and blood volume stimuli. Some “mixed” neurons, which secrete both CRH (corticotropin-releasing hormone) and vasopressin, terminate at the anterior pituitary corticotropic cells (Fig. 1).
4.3. Vasopressin receptors

Vasopressin exerts its action through two types of receptors (Table 1): the V1 or V1a receptors, mainly located in smooth muscle fibre, which enable vasopressin to exert its pressor action, whereas activation of the pituitary V3 or V1b receptors, stimulates the secretion of ACTH through an increase of cytosolic calcium; the V2 receptors, mainly located at the renal collecting tubule, exert an antidiuretic action, which is mediated, via an increase of cyclic AMP, through water channels. Located at the luminal (aquaporin 2) or blood (aquaporins 3 et 4) sites, these channels allow the reabsorption of pure water. The existence of extrarenal V2 receptors, the location of which have not been identified, is also suspected. Indeed, the infusion of a pure V2 receptor agonist, such as desmopressin, increases factor VIII, Von Willebrand factor, plasma renin activity and heart rate and leads to hypotension through its vasodilator action. These properties were used to determine the origin of nephrogenic diabetes insipidus [16].

4.4. Function

ADH is a hormone whose primary function, at physiological concentrations, is to regulate the water balance through the retention of pure water (independent of any sodium excretion). In addition to this retention of pure water, antidiuretic hormone regulates the blood volume through its vasopressor action. Lastly, it participates in the regulation of the ACTH feedback-loop, modulation of the autonomic nervous system activity and adaptation to stress in states of shock.

4.5. Regulation

4.5.1. Osmoregulation

The control of vasopressin secretion is exerted by an osmotic stimulus that depends on the serum sodium concentration, as well as that of serum glucose and urea. The plasma osmolality (in mOsm/kg of water) may be measured or estimated through the calculation of plasma osmolarity (in mOsm/L of water). The calculated osmolality (in mOsm/L) is equal to 2 (Na + K) (mmol/L) + [serum glucose(g/L) × 17] + [urea (g/L) × 5.5]. The rise in plasma osmolality activates the hypothalamic osmoreceptors, thus inducing ADH release on one hand, and thus pure water retention, and increased thirst on the other hand, stimulating the consumption of drinks (Fig. 1). These osmoreceptors are located in the hypothalamic circumventricular organs and are capable of detecting a 1 to 2% variation in plasma osmolality. Their nature was still unknown until recently, but the genetic analysis of different species of mice presenting with variable serum sodium levels enabled the identification of the NALCN sodium channel. A KO mouse that was heterozygous for this gene presented hypernaetraemia [17].

4.5.2. Blood volume regulation

The second stimulus of ADH secretion is the blood volume. A 10% decrease in blood volume leads to an increase in vasopressin, which is incidentally already perceptible during measurement of the hormone in a lying position and after 2 hours of orthostatism. The standing position in fact results in relative hypovolaemia, which stimulates vasopressin.

4.5.3. Other stimuli

There are however other non-osmotic stimuli of vasopressin such as nausea, pain, stress, hypoglycaemia, hypoxia, some cytokines, like interleukin-6, brain natriuretic peptide (BNP), oxytocin, and some neurotransmitters.

4.6. The regulation of water metabolism: synergism

The regulation of water metabolism is carried out not only by ADH, which is the only hormone that retains pure water, but also by aldosterone, which promotes water-sodium retention, and by the atrial natriuretic peptide (ANP), which predominantly enables sodium excretion.

Aldosterone secretion is stimulated by hyperkalaemia, hypovolaemia and ACTH, whereas ANP secretion is stimulated by vasopressin, aldosterone, cortisol and the thyroid hormones (Fig. 1).

Natriuresis, which is preserved in SIADH, is mainly attributed to the secretion of natriuretic hormones such as ANP.

4.7. New data on osmoregulation, metabolism and stress: neuroendocrine-pancreatic pathway

Exercise and metabolic stress lead to an increase of interleukin-1β, which stimulates the secretion of interleukin-6, which is itself capable of reprogramming the alpha cells to secrete GLP-1 (glucagon-like peptide 1). GLP-1 stimulates insulin secretion and could promote the transdifferentiation of alpha cells to beta cells [18]. In addition, by attaching to the receptors of the pro-opiomelanocortin (POMC) neurons, GLP-1 activates the melanocortin system, which is anorexigenic and increases lipolysis and beta-oxidation of fatty acids. It is also capable of increasing the concentration of some endocannabinoids and PPAR-gamma ligands. Interleukin-6 (IL-6) and stress stimulate vasopressin, which itself activates the corticotropin feedback-loop and stimulates ANP. ANP possesses receptors
in the pancreas and modulates the beta function by increasing insulin secretion and the mass of pancreatic beta cells [19], [20]. There is thus a synergistic action between stress and IL-6 on the metabolic pathway and on the water-sodium balance by means of joint action on the melanocorticotropin and vasopressinergic pathways.

5. Positive diagnosis of SIADH

The criteria for SIADH diagnosis are listed in Table 2. The main diagnostic criterion is hyponatraemia, specifically that which is euvoalaemic hypoosmolar (Fig. 2).

### Table 2
Antidiuresis syndrome or normovolemic hypoosmolar hyponatraemia.

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatraemia &lt; 135 mmol/L and decreased plasma osmolality &lt; 275 mOsm/kg</td>
</tr>
<tr>
<td>Inappropriate urine osmolality &gt; 100 mOsm/kg</td>
</tr>
<tr>
<td>Preserved natriuresis &gt; 30 mmol/L with normal sodium diet</td>
</tr>
<tr>
<td>Clinical euvoalaemia</td>
</tr>
<tr>
<td>Absence of renal, adrenal, thyroid insufficiency</td>
</tr>
<tr>
<td>No use of diuretics in the preceding week</td>
</tr>
<tr>
<td>Uricaemia &lt; 40 mg/L (0.24 mmol/L)</td>
</tr>
<tr>
<td>Azotemia &lt; 0.1 g/L (3.57 mmol/L)</td>
</tr>
</tbody>
</table>

### Table 3
Clinical symptoms of antidiuresis syndrome.

<table>
<thead>
<tr>
<th>Serum sodium (mmol/L)</th>
<th>Symptoms</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 125</td>
<td>Asymptomatic anorexia, nausea, vomiting</td>
<td>?</td>
</tr>
<tr>
<td>120–124</td>
<td>Confusion, cramps, headaches, balance and Cognitive disorders</td>
<td>23</td>
</tr>
<tr>
<td>115–119</td>
<td>Stupor</td>
<td>30</td>
</tr>
<tr>
<td>&lt; 114</td>
<td>Coma, seizures</td>
<td>40</td>
</tr>
</tbody>
</table>

Symptoms, morbidity, mortality related to the degree of hyponatraemia, the rapidity of onset, duration.

5.1. Clinical diagnosis

The blood pressure and heart rate in SIADH are normal. There is no skin tenting and no oedema [8,21].

5.1.1. Factors of severity

The clinical manifestations of SIADH, which are insidious, are often difficult to assess in patients with unknown histories. When above 125 mmol/L, SIADH is usually considered asymptomatic. The clinical risk, mainly neurologic, is especially great with hyponatraemia below 120 mmol/L, particularly in the presence of hypoxia, hypotension or dehydration, and even more so.

Fig. 2. Hyponatraemia diagnosis.
• measurements of urine aquaporin 2, which would reflect exaggerated antidiuresis induced by AVP, and copeptine, a stress marker that is co-secreted with AVP;
• sodium Holter through fluorescence sensor;
• assessment of blood volume through measurement of the total water by impedance analysis, which has been well demonstrated to have a good correlation with measurement by the deuterium reference method.

6. Differential diagnosis of hyponatraemia

The different parts of the differential diagnosis are summarised in Fig. 2 and are based on the calculation of plasma osmolarity and the clinical assessment of blood volume.

6.1. Normoosmolar and hyperosmolar hyponatraemia

Normoosmolar hyponatraemia is generally a form of hypertriglyceridaemia, which is still called pseudohyponatraemia, whereas hyperosmolar hyponatraemia is usually associated with major hyperglycaemia.

6.2. Hypovolaemic hypoosmolar hyponatraemia

When there is increased urine osmolality and hypovolaemia, it is generally a state of extracellular dehydration via sodium loss of gastrointestinal, central nervous, renal or cutaneous origin.

6.2.1. Salt loss of gastrointestinal origin

Salt loss of gastrointestinal origin is very common: diarrhoea, vomiting, fistulas and aspirations. Some forms are however more subtle to diagnose, such as those seen in patients with ileocolostomies; during periods of decompensation with significant sodium loss via the ileostomy, hyponatraemia with hyperkalaemia is revealed, mimicking acute adrenal insufficiency. Plasma hormone measurements paradoxically appear to reflect aldosterone resistance (increased serum aldosterone and plasma renin activity). This resistance is explained by the disappearance of colonic mineralocorticoid receptors, leading to an acquired pseudohypoaldosteronism induced by the colectomy [25].

6.2.2. Salt loss of central origin

Salt loss of central origin occurs when there is a cerebral lesion, notably in one-third of subarachnoid haemorrhage cases. They are associated with a higher ANP plasma concentration from the first day of the episode. This observation could be a factor of severity, justifying early management, since this salt loss could worsen the ischaemic neurological deficit [26]. The consequences of electrocution [27] and limbic encephalitis [28,29] can also result in these syndromes of salt loss of central origin. Salt loss syndromes, with their decreased blood volume, must be differentiated from SIADH, in which the blood volume is normal.

### Table 4

<table>
<thead>
<tr>
<th>Water load test: guidelines and interpretation criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drink 20 mL of water per kg of body weight at 8:00 in the morning, over 30 minutes</strong></td>
</tr>
<tr>
<td>In a fasting subject who has emptied one’s bladder</td>
</tr>
<tr>
<td><strong>Normal test</strong></td>
</tr>
<tr>
<td>Excretion of 3/4 of the overload by the 4th hour of the test (at noon)</td>
</tr>
<tr>
<td>Urine osmolality &lt; 100 mOsmol/kg; positive CH₂O from the 2nd hour of the test (at 10:00)</td>
</tr>
<tr>
<td>Reduction of plasma vasopressin values from the induced hypoosmolality effect</td>
</tr>
<tr>
<td><strong>Risk of false positives</strong></td>
</tr>
<tr>
<td>Unrecognized extracellular dehydration</td>
</tr>
<tr>
<td>Oedema</td>
</tr>
<tr>
<td>Urine retention (prostate adenoma, autonomic neuropathy)</td>
</tr>
</tbody>
</table>

if the disorder began suddenly and continued for an extended duration (Table 3). Hyponatraemia that begins rapidly in less than 48 hours can lead to early cerebral oedema.

5.1.2. Recent advances concerning the effects of moderate hyponatraemia

Recent studies have drawn attention to the manifestations of moderate hyponatraemia:

- **attention and gait disorders**, assessed and quantified by specific tests, are present when the mean serum sodium is around 128 ± 3 mmol/L compared to a eunatraemic control group. Hyponatraemia between 120 and 125 is accompanied by an increased risk of falling (21% of patients presenting this symptom), with a relative risk multiplied by 67 [22];
- **rhabdomyolysis**, in which an increase of plasma concentrations of muscle enzymes (CPK) is common. Whether acute or chronic, it occurs with signs of myopathy, which could result in falls [23];
- lastly, chronic hyponatraemia increases the **risk of fractures** due to the increased risk of falls. In addition, there is an increased risk of osteoporosis both in animals and in vitro models through modification of sodium/calcium exchanges [5,24].

5.2. Biological diagnosis

The biological diagnosis of SIADH, which is still sometimes called dilutional hyponatraemia, is based on the criteria summarised in Table 2. Keeping in mind that the free water clearance (CH₂O in millilitre per minute) is equal to the urine flow in ml/min × (1–(urine osmolality/plasma osmolality)), with osmolality expressed as mOsm/kg of water.

In the case of borderline hyponatraemia, a dynamic examination in the form of a water-loading test can be done. The performance guidelines and the interpretation criteria are shown in Table 4.

Other techniques of evaluation are under consideration, such as:
6.2.3. Salt loss of renal origin
Salt loss of renal origin is a differential diagnosis for salt loss of central origin. The salt loss is renal in both cases, but the primary cause is a central nervous system lesion in central causes, with the kidney then being only the effector. A primary renal lesion, a tubulopathy, the use of diuretics, peripheral adrenal insufficiency or isolated hypoaldosteronism are the causes of salt loss of renal origin, as well as of pseudohypoaldosteronism [30–33]. Isolated hypoaldosteronism of the elderly subject, the causes of which are poorly understood, is accompanied by hypersecretion of vasopressin that is secondary to the hypovolaemia induced by the primary hypoaldosteronism (Table 5). The diagnosis is based on the measurement of plasma renin activity and aldosterone after verification of normal serum cortisol and ACTH levels, as well as the absence of medication use that could interfere with the measurements [32,34,35].

6.2.4. Hyponatraemia from excessive sweat loss
Hyponatraemia from excessive sweat loss has been reported via profuse sweating in hot countries. There are however also recessive, autosomal genetically determined forms:

- cystic fibrosis related to a mutation of the CFTR gene, which is manifest by hyponatraemia after heat exposure in adults [36,37];
- hyperhydrosis from mutation of carbonic anhydrase 12, resulting in infantile dehydration, which is more or less severe with weaning failure, hyperkalaemia, a positive sweat test and failure to thrive with traces of salt on the skin after sweating [38,39].

6.3. Hypervolaemic hypoosmolar hyponatraemia
Hypovolaemic hyponatraemia with an apparently increased blood volume is found in states of oedema related to cirrhosis, nephrotic syndrome or heart failure. The true blood volume is however reduced, which explains the secretion of ADH adjusted for the real blood volume, even if it is inappropriate for the plasma osmolality.

6.4. Euvolaemic hypoosmolar hyponatraemia
SIADH is a euvolaemic, hypoosmolar hyponatraemia, and glucocorticoid insufficiency and hypothyroidism must first be ruled out.

6.4.1. Corticotropin deficiency
Corticotropin deficiency is diagnosed through measurement of serum cortisol and ACTH at 8:00 in the morning or during an emergency work-up. For normal values, an ACTH stimulation test should be requested under conditions with no stress, generally a few weeks after the hyponatraemic episode. Corticotropin deficiency is accompanied by increased vasopressin secretion due to absence of the restriction that ACTH normally exerts on its secretion. Hyponatraemia is also related to the reduction of glomerular filtration, while vasopressin secretion is stimulated by the hypoglycaemia and hypotension observed in these situations. It is especially crucial to measure the serum cortisol in the event of acute cerebral conditions.

6.4.2. Peripheral hypothyroidism
Peripheral hypothyroidism is only accompanied by hyponatraemia in the severe forms of the disease, generally characterised by myxoedema. The diagnosis is based on the TSH assay. Peripheral hypothyroidism is accompanied by a reduction in glomerular filtration with alteration in the dilution ability of the kidneys. There is a blood volume stimulus, which leads to an increase in vasopressin in myxoedema coma, as well as an increase in the renal expression of aquaporin 2.

6.4.3. Anterior hypopituitarism
The combination of corticotropin and thyrotropin deficiency, as observed in anterior hypopituitarism, can generally be manifest by hyponatraemia. In this situation, it is therefore recommended to measure not only the serum cortisol and TSH, but also FT4.

7. Aetiological diagnosis of SIADH
The aetiological diagnosis of SIADH must first rule out endocrine causes requiring a specific treatment. After exclusion of these endocrine diseases, the four most classic causes of SIADH are drugs, lung disease, neurologic disorders and malignancies.

7.1. Iatrogenic causes
Iatrogenic causes must always be considered due to their frequency and the simplicity of their treatment (Fig. 3). Certain drugs are very common, such as neuroleptics; antidepressants, in particular selective serotonin reuptake inhibitors; chemotherapy; carbamazepine; and diuretics. These latter lead to sodium/water depletion due to hypersecretion of vasopressin relative to the hypovolaemia. The administration of oxytocin to women in labour can also induce SIAD due to the closeness in the structure of the two hormones, which differ by only two amino acids. Vasopressin analogues also can cause SIAD, not only in cases
of overdose but also under special circumstances, for instance with the administration of desmopressin:

- in children with enuresis, especially when this drug is combined with oxybutynin, which is an anticholinergic [40];
- during surgery associated with minor coagulation disorders, such as Von Willebrand factor deficiency, haemophilia A or platelet dysfunction. Cases of acute water intoxication have also been reported [41,42]. In a series of 140 treated cases, 70 cases of hyponatraemia, six of which had seizures, were identified;
- similarly, the use of terlipressin to control bleeding of oesophageal varices [43] can lead to water intoxication.

CYP3A4 inhibitors (valproic acid, amiodarone, diltiazem, verapamil, erythromycin, azithromycin, itraconazole, ketoconazole, miconazole, bortezomib, imatinib, erlotinib, afiblercept (anti-VEGF), capetibicine, vorinostat gemcitabine, seliciclib and flavopiridol, eribulin and sapanpoline, bevacizumab, EME2, mTOR inhibitor linezolid) are capable of inhibiting the metabolism of inhaled corticosteroids (budesonide), thus inducing clinical pseudo-Cushing syndrome. The plasma concentrations of cortisol and ACTH fall drastically, resulting in hyponatraemia, which self-corrects on glucocorticoid supplementation, but especially with the discontinuation of drugs that are likely to interfere [44,45].

7.2. Neurologic causes

Practically all neurological disorders are likely to induce SIADH through osmoreceptor alteration. Among these disorders, limbic encephalitis of infectious (herpes), paraneoplastic (lung or testicular cancers, lymphomas, thymomas), and autoimmune or genetic origins has drawn attention. It combines short-term memory disorders, which are often subacute, with cognitive alterations, temporal epilepsy and hyponatraemia. Temporal anomalies are noted on EEG and cerebral MRI. Antibodies may be found.

7.3. Lung disorders

Lung disorders are able to stimulate the secretion of vasopressin through changes in intrathoracic pressures, thereby stimulating the blood volume receptors, or by reducing the inhibitor effect exerted by the vagal nerve [46].

7.4. Malignant tumours

Of the malignant tumours, small-cell lung cancer induces SIADH in 10 to 60% of cases. Squamous cell lung cancers and non-lung cancers are more rarely the cause. The severity of SIADH is proportional to the degree of cancer spread; some studies make it seem that SIADH is always present but that its expression varies according to a continuum. SIADH may precede the appearance of the tumour by several months. Hyponatraemia by itself is a negative prognosis factor. In small-cell lung cancers, vasopressin secretion is observed in 50% of cases, oxytocin in 50% of cases, and both hormones in 50% of cases. Hyponatraemia can also occur after chemotherapy. It was demonstrated in vitro that tumour cells were capable of producing AVP through detection of messenger RNA [47]. But the tumour mass itself can be a factor of SIADH of lung origin. Other cancers that are likely to result in SIADH are neuroendocrine carcinomas of the urinary (prostate, bladder, ureter) and digestive tract (pancreas, duodenum, stomach, colon; breast;
7.5. Rare causes

Rarer causes of antidiuresis syndrome have also been identified:

- **the nephrogenic syndrome of inappropriate antidiuresis or SIAD from X-linked disease caused by an activating mutation of the V2 receptor** results in spontaneous episodes, usually transient, of hyponatraemia within the same family. The anomalies are sometimes only detectable by water overload. These cases of SIAD resist V2 receptor antagonists and respond to water restriction and urea [48,49];
- **hyponatraemia of marathon runners** could be related to excessive hydration together with AVP secretion stimulated by non-osmotic routes, i.e., pain, hypovolaemia, interleukin-6 correlated with a rise in muscle enzymes (CPK). This hyponatraemia is accompanied by a risk of fatal cerebral and pulmonary oedema in 1% to 5% of hyponatraemia cases of distance runners [49–51]. The extent of these manifestations is however variously estimated (0 to 50% of ultra-marathoners) [52]. The benefit of studying marathon runners lies in the knowledge that could be gained of the relationships between osmoregulation and metabolism (see Pathophysiology chapter);
- **lastly, infections related to the human immunodeficiency virus (HIV)** may be accompanied by SIAD related to adrenal insufficiency, particularly from interferences between many antiretrovirals, cytochrome p450 inhibitors and budesonide, and/or infections such as Pneumocystis carinii pneumonia or central nervous system disorders;
- **the acute crisis of intermittent acute porphyria** can also be accompanied by hyponatraemia.

7.6. A special case: acute water intoxication

Acute water intoxication or hypoosmolar hyponatraemia with low urine osmolarity is a severe hyponatraemic event (<115 mmol/L), occurring after the massive ingestion of hypotonic drinks. A water intake over 25 ml/kg is equivalent to the maximum renal excretion, and favours hyponatraemia. Mechanisms are still poorly understood. The scenario is frequently encountered in chronic psychosis, which itself might be associated with genetic susceptibility [53,54]. Orexin gene anomalies can affect polydipsia syndromes of schizophrenic patients. Frequent tobacco intoxication in these patients is also a stimulus of vasopressin secretion via the nicotine. An episode of primary polydipsia or compulsive thirst of behavioural or biochemical origin related to a peak in dopamine, could induce an acute water intoxication. Primary transient or iatrogenic hypersecretion of vasopressin could also lead to this water intoxication. Renal hypersensitivity to vasopressin or oxytocin has been suggested. The excessive water consumption may be increased by the sensation of mouth dryness that is triggered by psychoactive drugs that also cause vasopressin hypersecretion, increasing the risk of these water intoxication episodes by three-fold [55]. Beer drinker syndrome is a variant, with beer being a very hypotonic beverage.

Finally, cases of water intoxication have been reported from excessive water intake during pelvic ultrasounds [56,57], coloscopies [58], or hypotonic irrigations during gynaecological or prostatic surgery [59,60].

8. Treatment

All cases of hyponatraemia are not related to SIADH, and an accurate diagnostic approach is essential to proper treatment. Hyponatraemia treatment is based on glucocorticoids in case of adrenal insufficiency, whether from primary adrenal or pituitary origin. Mineralocorticoids in isolated hypoaldosteronism; discontinuation of iatrogenic drugs, particularly diuretics and psychoactive drugs; and isotonic saline fluid in case of salt loss. SIADH treatment is currently based on water restriction, demeclocycline and vasopressin receptor antagonists, which have yet to arrive in France. Other treatments for SIADH have been suggested: ethanol, urea, prostaglandin inhibitors, phenytoin, and some chemotherapies.

8.1. Emergency treatment of severe hyponatraemia

Any serious hyponatraemia, i.e., generally less than 115 mmol/L and/or if accompanied by neurological signs such as coma or seizures, requires urgent treatment based on:

- 20% hypertonic saline fluid;
- generally administered via intravenous syringe pump, at the rate of 50 ml per 12 hours;
- to be administered under close monitoring with serum electrolyte panel every six hours;
- this infusion of hypertonic saline fluid will be stopped once the serum sodium reaches 120 mmol/l;
- the rate of correction must never exceed 12 mmol/24 hours (0.5 mmol/hour) in order to avoid central pontine myelinolysis, which is manifest as pseudobulbar palsy.

Some recent studies [61] showed the protector effect of minocycline in rats with regard to the risk of central pontine myelinolysis.

8.2. Guidelines for care of SIAD

8.2.1. Water restriction

Water restriction remains a treatment that is not costly and not toxic, but its efficacy depends on the strictness of the restriction, for it is often poorly accepted by patients, especially in the long-term.

For example, a serum sodium concentration less than 120 mmol/L must result in a water restriction of 100 ml/24 hours; from 120 to 125 mmol/L: 300 ml/24 hours; from 125 to 130 mmol/L: 500 ml/24 hours; and from 130 to 135 mmol/L: 700 ml/24 hours.
8.2.2. Demeclocycline

Demeclocycline is a tetracycline that was remarketed by Genopharm.

8.2.2.1. Characteristics. It has a half-life of 12 hours, with elimination via urine and stool. It acts by inducing nephrogenic diabetes insipidus, independent of the water intake, through post-receptor effect. It is available in 150 mg oral gel capsules with an initial hospital prescription. The initial therapy is 900 to 1500 mg/day for ten days, with a moderate water restriction. Lower doses (600 mg/day) are recommended as initial therapy as well as maintenance therapy in elderly subjects, without water restriction. This treatment requires monitoring of the serum sodium, urea and creatinine.

8.2.2.2. Indications. Demeclocycline is indicated in cases of serum sodium less than 125 mmol/L or if the patient is symptomatic, or in cases of resistance to water restriction, regardless of the origin of the hyponatraemia (SIADH of neoplastic, iatrogenic or heart failure origin). It is a fairly expensive drug and is reimbursed 65% by the national health insurance in France. The national Transparency Commission considered that it improved the therapeutic value in non-comparative studies, some older, which included a small number of patients (seven to 17). A follow-up study was requested [62–64].

8.2.2.3. Side effects. Side effects include tooth discolouration or hypoplasia of the enamel in children under 8-years-old; risk of photosensitivity and allergies; digestive disorders; haematological disorders; dose-dependent renal failure, which is reversible upon discontinuation; phosphate diabetes [65]; polyuria with risk of hypernatraemic intracellular dehydration if the associated water restriction is severe.

8.2.2.4. Contraindications. The contraindications include kidney failure, hepatocellular failure, age less than 8 years, pregnancy, breastfeeding, asthma, severe uncontrolled hypertension and oral retinoids since they increase the risk of intracranial hypertension. Combinations with the following must be avoided: all nephrotoxic drugs; sun exposure; anticoagulants; iron intake or anti-acid gastrointestinal drugs, which reduce absorption. Demeclocycline can increase the selection of resistant bacteria.

8.2.3. Aquaretics

8.2.3.1. Classification. Aquaretics are non-peptide vasopressin receptor antagonists, which, contrary to the peptide antagonists, are effective in humans and have a longer half-life and the possibility of oral administration (Table 6). None of these therapies are marketed in France in 2011.

These include V1a and V2 receptor antagonists, such as conivaptan, which is marketed under the name Vaprisol® by the firm Yamamushi. This drug, which was authorized by the Food and Drug Administration in the USA, is administered intravenously or orally but only in the hospital setting since it is a CYP3A4 cytochrome inhibitor. It was tested in heart failure and obtained a marketing authorization in the United States.

Pure, orally administered V2 receptor antagonists were tested in SIADH, cirrhosis, and as the preceding, in heart failure. The leader is tolvaptan, marketed under the name Samsca by the firm Otsuka, which should obtain a marketing authorisation in France. Other V2 receptor antagonists are under development: lixivaptan or VPA485 from Pfizer and Wyeth-Ayerst; satavaptan (Sanofi); and mozavaptan, studied only in cirrhosis and marketed under the name Physuline® in Japan since 2006.

8.2.3.2. Side effects. The potential complications of V2 receptor antagonists are central pontine myelinolysis, from a too rapid correction of serum sodium (this has however never been reported with the antagonists); and hypotension, particularly if the hyponatraemia includes a hypovolaemic component. The long-term toxicity, particularly neurological, is not entirely known.

These drugs are contraindicated in pregnant or breastfeeding women, in cases with hypovolaemia and of course, in adrenal insufficiency.

They can induce drug interactions, since they are P3A4 cytochrome inhibitors that slow the metabolism of drugs such as ketoconazole, statins, amiodipine, midazolam and warfarin, increasing the duration of action of these therapies.

8.2.3.3. Efficacy. The efficacy of the aquaretics in SIADH was tested for conivaptan and tolvaptan over a period of 4 to 30 days in double-blind randomised versus placebo studies. These antagonists induce a significant increase in the serum sodium due to an increase in the free water clearance. In one of the studies, an increased sensation of well-being and ability to concentrate urine were also noted. It seems that these studies however had multiple biases, and so their efficacy was unable to be ascertained. The side effects included polydipsia, hypotension and hypovolaemia. There was no difference in mortality between the treated group and the placebo group. These drugs can be combined with diuretics.

Table 6

<table>
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<tr>
<th>Hypersecretion of vasopressin and heart failure.</th>
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<td><strong>Mechanism</strong></td>
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<tr>
<td>Through reduction of cardiac output and peripheral vasodilatation</td>
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<td>AVP is a vasopressor and worsens the disease progression by increasing vascular resistance</td>
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<tr>
<td><strong>Benefit of V2 receptor antagonists</strong></td>
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<tr>
<td>Conivaptan [72]: 1 single intravenous dose (10 to 40 mg) in 142 patients: increase of diuresis within 6 hours</td>
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<tr>
<td>Tolvaptan</td>
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<tr>
<td>30 to 60 mg orally 1 month in 245 patients: weight loss and increase in serum sodium [73]</td>
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<tr>
<td>30 mg/day orally for &gt; 60 days vs. placebo, n=4000 total: significant weight loss, clinical improvement but no decrease in mortality [74]</td>
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<tr>
<td>Satavaptan</td>
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<td>25 to 50 mg orally for 4 days, double-blind vs. placebo (n = 118) then open trial for 1 year; effective for increase in serum sodium (even sometimes too rapid) [75]</td>
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<tr>
<td>Lixivaptan</td>
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<tr>
<td>Balance study ongoing (stage III-IV), randomised, double-blind versus placebo</td>
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Tolvaptan was continued up to 200 weeks in an open extension of the study, which demonstrated cognitive improvement in the patients, but not on the physical level. Indeed, survival did not improve, whether with euvoalaemic or hypervolaemic SIADH.

8.2.3.4. Risk-benefit ratio. These results prompted a re-evaluation of the risk of mortality in patients with hyponatraemia in very recent studies (see Prognosis) on euvoalaemic (SIAD) or hypervolaemic (chronic kidney and heart failure) hypoosmolar hyponatraemia. Higher mortality was found in the hyponatraemic patients, without knowledge of whether this hyponatraemia was the cause or the consequence of the disease.

Indeed, the use of V2 receptor antagonists in heart failure was justified by the reduction in cardiac output and peripheral vasodilatation. The main studies demonstrating results of use of the V2 receptor antagonists in heart failure are shown in Table 6. Otherwise, disturbances in free water excretion are present in cirrhosis, even in the absence of spontaneous hyponatraemia, justifying the use of V2 receptor antagonists in this setting. The mechanisms are a non-osmotic stimulus related to vasodilatation, reduced glomerular filtration and decreased clearance of antidiuretic hormone.

8.2.4. Other SIADH treatments

Other substances have been used in the treatment of SIADH: urea, ethanol, prostaglandin inhibitors and chemotherapy.

8.2.4.1. Urea. Urea, at a dose of 30 to 60 g per day (0.5 to 1 g/kg orally or via gastric tube) was effective in the long-term in a series of patients, although small (n = 20). It did not have side effects and required no water restriction. It acts by inducing osmotic diuresis, but the published studies do not include a randomised trial and were associated with isotonic saline fluid [66].

8.2.4.2. Ethanol. Ethanol is also a substance that increases diuresis and decreases vasopressin by resetting the osmostat threshold. These effects were demonstrated in 1942 [67] and were able to be brought about clinically [68], although the effects of alcohol made its use difficult in practice.

8.2.4.3. Prostaglandin inhibitors. Prostaglandin inhibitors, such as indomethacin 200 mg per day, possibly combined with 1.5 g of aspirin, equally improves the free water clearance in the central types of SIADH, although again the toxic effects themselves, particularly gastric-related from the non-steroidal anti-inflammatory drugs, may limit their use in practice [69].

8.2.4.4. Chemotherapy. Chemotherapy is naturally effective in SIADH related to tumour secretion [70], although it can have a hyponatraemic effect of its own.

8.3. Therapeutic indications of SIAD

8.3.1. Pro and cons of available treatments

In the end, treatment of SIADH remains difficult. Isotonic saline fluid is ineffective in the euvoalaemic and hypervolaemic hypoosmolar forms of hyponatraemia. At high doses, hypertonic saline fluid can correct the hyponatraemia too rapidly, thus creating a risk of myelinolysis. Water restriction acts slowly, and its compliance is difficult. The response to demeclocycline is variable and slow, and it is potentially nephrotoxic. Fludrocortisone was able to be used in a single study on SIADH, but it cannot be used if there is already sodium and water retention. Urea is not marketed and has an unpleasant taste.

AVP receptor antagonists, such as conivaptan, are for intravenous hospital use only due to their CYP 3A4 cytochrome inhibitor properties. They can cause a local reaction and are currently only available in the USA. Questions regarding the use of aquaretics remain, although they seem to be useful for the correction of euvoalaemic and hypervolaemic hyponatraemia such as in SIADH [71,23], heart failure [72–75], and cirrhosis [76]. It can be a diagnostic test, be combined with diuretics and seems to improve the quality of life by enabling the water restriction to be lifted and to use cisplatin in chemotherapy if necessary [77].

8.3.2. Treatment of specific situations

Hypervasopressinism secondary to isolated hypoaldosteronism is usually related to a non-osmotic stimulus that is easy to correct through reestablishment of the proper fluid volume, by increasing the sodium intake and giving fludrocortisone.

In cases of salt loss of central origin, the administration of intravenous saline fluid aims to correct serum sodium levels at a rate not exceeding 0.5 mmol/hr. Fludrocortisone can be added if subarachnoid haemorrhage is at risk of causing vasospasm. Water restriction has no role in this scenario. Hydrocortisone may be useful.

8.3.3. Treatment according to the severity of hyponatraemia

Finally, in cases of severe or recent (less than 48 hours) clinical symptoms, such as coma, seizures or respiratory distress, the first treatment remains 20% hypertonic saline fluid.

If the symptoms are more moderate, such as nausea, confusion, disorientation or balance disorders, hypertonic saline fluid is also used. Tolvaptan (15 to 60 mg orally) should provide a benefit when it is available.

When symptoms are moderate or absent (mild cognitive disorders, depression), water restriction remains necessary, together with first-line use of demeclocycline, or aquaretics when available.

Correction of severe hyponatraemia must always be carried out slowly (less than 12 mmol/24 h or 18 mmol/48 h). Serum sodium must be monitored every 6 hours, particularly in the beginning. It is important to correct all the other causative factors.

The need for chronic treatment must be assessed according to the impact of the ailment.

9. Conclusion

In conclusion, all cases of hyponatraemia require a medical history, a thorough physical examination noting signs of dehydration or conversely, hypervolaemia. The ongoing treatment must be carefully specified.
Positive diagnosis is based on the analysis of measured or calculated plasma osmolality and the assessment of blood volume. All forms of hyponatraemia are not relative to SIADH, and SIADH, or better SIAD, is a form of plasma hypoosmolality with preserved urine osmolality and without hypovolaemia and kidney, adrenal or thyroid insufficiency. TSH and FT4 on one hand and serum cortisol and ACTH on the other must be measured in all cases of hyponatraemia, to rule out an endocrine cause that is easily treatable, such as hypothyroidism or especially adrenocortical insufficiency of peripheral or central origin. It is also important to rule out neoplasia, particularly of the lung or brain, knowing that hyponatraemia can sometimes precede the discovery of a neoplasm; hyposcretion of renin or aldosterone, which is easily treatable with fludrocortisone; and salt loss of central origin, in which the circumstances of occurrence are generally suggestive of the cause. Finally, unexplained SIADH remains fairly rare, as hyponatraemia is often multifactorial in origin. Hypertonic saline fluid in the most severe cases, water restriction and demeclocycline in the chronic forms remain the most easily available treatments. The marketing of vasopressin receptor antagonists should facilitate the management of these situations.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


