Sodium disturbances are common in patients with brain injury because of the major role that the central nervous system plays in the regulation of sodium and water homeostasis. In addition, treatment of the injured brain can itself disturb regulation of sodium and water. Sodium disturbances can lead to serious complications and adverse outcomes, including death. Complications can be minimized by a systematic approach to recognition, diagnosis, and treatment of the sodium disturbance.

**Regulation of salt and water balance**

Sodium is the major extracellular cation and one of the most important osmotically active solutes. The extracellular to intracellular fluid sodium concentration gradient is maintained by the sodium–potassium ATPase pump and total body sodium is controlled by renal excretion. Sodium is freely filtered at the glomerulus and the majority is reabsorbed at the proximal tubule under the control of sympathetic nerves and atrial (ANP) and brain (BNP) natriuretic peptides.1 The latter cause natriuresis by inhibition of sodium transport in the distal tubule and collecting duct of the kidney, and production of concentrated urine. Serum osmolality of around 280 mOsm kg⁻¹ stimulates ADH release and, at ~295 mOsm kg⁻¹, thirst is stimulated prompting increased water intake in conscious patients. ADH is also released in response to decreases in arterial pressure and intravascular volume that are detected by low-pressure baroreceptors in the right atrium and great veins and high-pressure baroreceptors in the carotid sinus. Hypovolaemia and hypotension also result in increased sympathetic activity and activation of the renin–angiotensin–aldosterone system.

Disturbance of sodium balance is a common finding in the adult hospital population. It is particularly common after brain injury when changes in sodium and water balance have profound effects on the injured brain.3 The symptoms and signs relate not only to the severity of the sodium disturbance (Table 1) but also to the rate of change of serum sodium concentration. Normal plasma sodium is 135–145 mmol litre⁻¹ and plasma osmolality 285–295 mOsm kg⁻¹.

**Hyponatraemia**

Hyponatraemia is defined as a serum sodium concentration of <135 mmol litre⁻¹ and occurs in up to 15% of the general adult inpatient population. It is more common after brain injury, especially in those patients who are critically ill,2 usually develops between 2 and 7 days after the injury and is associated with mortality increases of up to 60%.3, 4 Hyponatraemia is commonly associated with hypotonicity but may rarely occur in isotonic and hypertonic conditions.4 Hypotonic hyponatraemia develops in a number of cases in the brainstem and inhibition of thirst and salt appetite.

Because sodium concentration is a major determinant of serum osmolality, it is largely responsible for the normal regulation and distribution of total body water. In essence, total body water is controlled by renal manipulation of sodium with resulting water adjustment to maintain tonicity. Sodium and water balance are regulated primarily by serum osmolality but also by intravascular volume and pressure. An increase in extracellular fluid osmolality is detected by osmoreceptors in the hypothalamus that stimulate synthesis of arginine vasopressin, or antidiuretic hormone (ADH), in the supraoptic and paraventricular nuclei. ADH is then transported to, and released from, the posterior lobe of the pituitary gland. This results in reabsorption of water in the distal tubule and collecting duct of the kidney, and production of concentrated urine. Serum osmolality of around 280 mOsm kg⁻¹ stimulates ADH release and, at ~295 mOsm kg⁻¹, thirst is stimulated prompting increased water intake in conscious patients. ADH is also released in response to decreases in arterial pressure and intravascular volume that are detected by low-pressure baroreceptors in the right atrium and great veins and high-pressure baroreceptors in the carotid sinus. Hypovolaemia and hypotension also result in increased sympathetic activity and activation of the renin–angiotensin–aldosterone system.

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Disorders of sodium balance after brain injury

Table 1 Symptoms and signs of hyponatraemia and hypernatraemia

<table>
<thead>
<tr>
<th>Hyponatraemia</th>
<th>Hypernatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>Lethargy</td>
</tr>
<tr>
<td>Nausea, vomiting, and anorexia</td>
<td>Thirst</td>
</tr>
<tr>
<td>Irritability</td>
<td>Irritability</td>
</tr>
<tr>
<td>Headache</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Muscle weakness/ cramps</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Hypono reflexia</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Drowsiness and confusion</td>
<td>Hyperno reflexia</td>
</tr>
<tr>
<td>Seizures</td>
<td>Seizures</td>
</tr>
<tr>
<td>Coma</td>
<td>Coma</td>
</tr>
<tr>
<td>Death</td>
<td>Death</td>
</tr>
</tbody>
</table>

conditions (Table 2) and creates a gradient across the blood–brain barrier favouring entry of water into the brain and the development of cerebral oedema. The cause of the low serum sodium can be determined by the associated volume status.

Causes

Iatrogenic hyponatraemia is not uncommon and usually results from the administration of inappropriately hypotonic fluids, often in the postoperative period when ADH levels are raised as part of the stress response. However, after brain injury, hyponatraemia occurs most frequently because of the syndrome of inappropriate ADH secretion (SIADH) or the cerebral salt wasting syndrome (CSWS).3, 4

General treatment

The underlying cause of the hyponatraemia should be identified and treated. In the context of brain injury, an expectant and supportive treatment strategy is best in asymptomatic patients as sodium disturbances are often transient and self-limiting. Prompt treatment is indicated in the presence of acute symptomatic hypotonic hyponatraemia to minimize the risk of significant neurological complications and adverse outcome, including an increased risk of death. However, the correction of hyponatraemia can itself lead to neurological sequelae, particularly central pontine myelinolysis, and these risks should be minimized by gradual correction of sodium deficits. In most circumstances, serum sodium should be increased by no more than 0.5 mmol litre$^{-1}$ h$^{-1}$ or 8–10 mmol litre$^{-1}$ day$^{-1}$. Treatment should always be targeted to the point of alleviation of symptoms rather than to an arbitrary serum sodium concentration.

 Syndrome of inappropriate antidiuretic hormone

The most common neurological causes of SIADH are subarachnoid haemorrhage (SAH), traumatic brain injury (TBI), brain tumour, and meningitis/encephalitis. Drug-related hyponatraemia may also occur and anticonvulsant drugs, specifically carbamazepine, are of particular relevance after brain injury.

Pathophysiology

The pathophysiology of SIADH is not fully understood. However, ADH release is related to the threshold of the thirst response and there is a lower threshold for thirst in patients with SIADH.6 There is also loss of control of ADH release and plasma ADH concentration is unaffected by continued fluid administration/intake or by osmotic stimulus. ADH concentration is therefore inappropriately high in the context of the production of small volumes of concentrated urine.

Diagnosis

The diagnostic criteria for SIADH are:

(i) hypotonic hyponatraemia (serum sodium < 135 mmol litre$^{-1}$ and serum osmolality < 280 mOsm kg$^{-1}$);
(ii) urine osmolality > serum osmolality;
(iii) urine sodium concentration > 18 mmol litre$^{-1}$;
(iv) normal thyroid, adrenal, and renal function;
(v) clinical euvo lamia—absence of peripheral oedema or dehydration.

The absence of dehydration in SIADH is very important as this is the key feature differentiating it from CSWS in which clinical signs of dehydration will always be present (discussed later). It is important to distinguish between SIADH and CSWS because the treatment of the two conditions is diametrically opposed (Table 3).

Specific treatment

SIADH is often a self-limiting disease after brain injury and treatment should only be initiated if the patient is symptomatic, the serum sodium is significantly low or falling rapidly. Electrolyte-free water restriction, initially to 800–1000 ml day$^{-1}$, forms the mainstay of treatment of SIADH and usually results in a slow rise in serum sodium of 1.5 mmol litre$^{-1}$ day$^{-1}$. However, such a degree of fluid restriction can be difficult to achieve because it may be unpleasant for conscious patients, worsen cardiovascular instability, and increase the risk of cerebral ischaemia in critically ill patients.

Table 2 Common causes of hypotonic hyponatraemia

<table>
<thead>
<tr>
<th>Hypovolaemic hyponatraemia</th>
<th>Normovolaemic hyponatraemia</th>
<th>Hypervolaemic hyponatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSWS</td>
<td>SIADH</td>
<td>SIADH</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>Subarachnoid haemorrhage</td>
<td>Other central nervous system pathology</td>
</tr>
<tr>
<td>Drug induced</td>
<td>Pulmonary pathology</td>
<td></td>
</tr>
<tr>
<td>Diuretics (including osmotic)</td>
<td>Thiazide diuretics</td>
<td>Congestive cardiac failure</td>
</tr>
<tr>
<td>Ketonuria</td>
<td>Adrenal insufficiency</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Diarrhoea/vomiting</td>
<td>Hypothyroidism</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Sweating</td>
<td>Iatrogenic</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>Blood loss</td>
<td>Iatrogenic</td>
<td>Iatrogenic</td>
</tr>
</tbody>
</table>

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brain-injured patients. Hypertonic saline (1.8%) has a limited place in the treatment of SIADH but should be restricted to severely symptomatic acute hyponatraemia, particularly after SAH when fluid restriction is contraindicated. Hypertonic saline infusion should be discontinued when serum sodium reaches 120–125 mmol litre\(^{-1}\) and further management continued with fluid restriction.

Pharmacological treatment is an option when the diagnosis of SIADH is certain. Different classes of drugs are effective through different mechanisms.

(i) Increase in excretion of water with furosemide or other diuretics. Simultaneous saline or salt supplementation should be administered to replace the associated sodium loss.

(ii) Inhibition of the renal responses of ADH by demeclocycline or lithium. Demeclocycline is the least toxic and an initial daily dose of 900–1200 mg should be reduced to 600–900 mg per day after therapeutic effect is achieved, usually between 3 days and 3 weeks after starting treatment.

(iii) ADH-receptor antagonists, such as conivaptan and lixivaptan, inhibit the binding of ADH to renal receptors. They have been shown to be effective in small clinical trials by inducing aquarexis, the electrolyte-sparing excretion of free water.

### Cerebral salt wasting syndrome

CSWS is characterized by renal loss of sodium resulting in polyuria, natriuresis, hyponatraemia, and hypovolaemia occurring as a result of a centrally mediated process. It is predominantly associated with SAH and TBI but has also been described after brain tumour, ischaemic stroke, and TB meningitis. It usually occurs in the first week after brain injury and resolves spontaneously within 2–4 weeks. The exact incidence is uncertain because many cases of CSWS have probably been, and continue to be, mistakenly diagnosed as SIADH.

### Pathophysiology

CSWS was first described in 1950 and is related to disruption of hypothalamo-renal pathways.\(^7\) The precise pathophysiology is unclear, but raised levels of ANP and BNP are likely to mediate, at least in part, the natriuresis and hyponatraemia associated with CSWS, particularly after SAH.\(^8\) In addition, the increased sympathetic activity results in increased renal perfusion pressure and subsequent natriuresis.

### Diagnosis

The biochemical criteria for CSWS are:

(i) low or normal serum sodium;
(ii) high or normal serum osmolality;
(iii) high or normal urine osmolality;
(iv) increased haematocrit, urea, bicarbonate, and albumin as a consequence of hypovolaemia.

However, these criteria are often inconclusive. In CSWS, total daily urine sodium excretion is greater than intake, whereas it is usually equal to intake in SIADH, that is, overall sodium balance is negative in CSWS and generally neutral in SIADH.

Diagnosis is based on a careful examination in addition to biochemical investigations because biochemical criteria may fail to differentiate CSWS from SIADH (Table 3). The key clinical diagnostic factor is the presence of volume depletion after CSWS. Daily weight can offer information in this regard and examination of mucous membranes, skin turgor, capillary refill time, jugular venous pressure, and cardiovascular parameters (particularly orthostatic arterial pressure changes) should be undertaken. A thorough review of fluid balance charts will also demonstrate an overall negative balance.

Volume status can be difficult to assess clinically and may rarely also be a confounding factor. Hypovolaemia has been identified in some patients fulfilling the diagnostic criteria for SIADH and this occurs because the volume depletion of CSWS causes a secondary rise in ADH. However, under such conditions, the correct diagnosis is CSWS rather than SIADH.\(^3\)

### Specific treatment

The primary treatment of CSWS is volume and sodium resuscitation, although the saline solution used is more controversial. As a general rule, 0.9% saline is indicated in the first instance, although, in acute symptomatic hyponatraemia, hypertonic (1.8% or 3%) saline is recommended, with the concomitant administration of furosemide to minimize the risks of an overloaded circulation. It is of note that, in some patients with CSWS, administration of sodium may actually increase the natriuresis and associated water loss, and worsen the clinical status. Once normovolaemia and normonatraemia have been restored, ongoing losses should be replaced with either i.v. saline or water and sodium tablets, until there is resolution of the CSWS. Close monitoring of fluid balance, serum sodium concentration, and total sodium balance should continue during this period.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Clinical and biochemical features of the SIADH and the CSWS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
<td>SIADH</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>Normal or increased</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Absent</td>
</tr>
<tr>
<td>Body weight</td>
<td>Increased</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>Positive</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>Increased</td>
</tr>
<tr>
<td>Serum sodium concentration</td>
<td>Low</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>Decreased</td>
</tr>
<tr>
<td>Urinary sodium concentration</td>
<td>High</td>
</tr>
<tr>
<td>Urinary osmolality</td>
<td>High</td>
</tr>
<tr>
<td>Sodium balance</td>
<td>Equal</td>
</tr>
<tr>
<td>Plasma urea and creatinine</td>
<td>Decreased or normal</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>Decreased</td>
</tr>
</tbody>
</table>
Disorders of sodium balance after brain injury

In some cases, CSWS may be refractory to standard therapy and fludrocortisone (0.1–0.4 mg daily) may limit the sodium loss by increasing sodium reabsorption from the renal tubule. Such treatment may cause hyperkalaemia and serum potassium should be closely monitored.

**Hypernatraemia**

Hypernatraemia is defined as a serum sodium of $>145$ mmol litre$^{-1}$. It occurs less commonly than hyponatraemia; its incidence is $\sim 1\%$ in the general inpatient hospital population and $9\%$ in the intensive care setting. It is more common in brain-injured patients and is often an indicator of the severity of the underlying disease. $^3$

**Causes**

Hypernatraemia is usually related to inadequate free water intake or excess water loss and only rarely with excessive salt intake. After brain injury, hypernatraemia is most commonly related to the development of central diabetes insipidus (DI) or the overzealous use of osmotic diuretics such as mannitol. Iatrogenic causes are relatively easy to recognize and manage and usually respond to normalization of sodium intake. Nephrogenic DI is also a cause of hypernatraemia in the general hospital population, but beyond the scope of this review.

**Diabetes insipidus**

DI is associated with TBI, SAH, intracerebral haemorrhage, and pituitary surgery. The incidence of DI can be as high as $35\%$ after TBI when it is associated with more severe injury and increased mortality. $^2$ Development of DI in non-pituitary surgery is often associated with severe, pre-terminal, cerebral oedema. DI is therefore a common finding after brain stem death and has particularly relevance in the management of the brain-dead organ donor. $^10$

**Pathophysiology**

DI results from a failure of ADH release from the hypothalamic-pituitary axis. The ability to concentrate urine is impaired resulting in the production of large volumes of dilute urine. This inappropriate loss of water leads to an increase in serum sodium and osmolality and a state of clinical dehydration.

The anatomical and pathophysiological basis of DI is relatively well understood. Damage or compromise of the hypothalamus above the median eminence may lead to permanent DI, whereas damage below this level, or disturbance of the posterior lobe of the pituitary gland, leads to transient DI because ADH can subsequently be released from nerve fibres ending in the median eminence. This explains why DI is transitory in some patients but not in others.

**Diagnosis**

In awake patients, the classic symptoms of polyuria, polydypsia, and thirst make the diagnosis of DI relatively straightforward. However, hyperglycaemia has similar symptomatology and should be excluded. It is important to distinguish between hypovolaemic hypernatraemia occurring because of water loss (e.g. dehydration or DI) and the rarer eu- or hypervolaemic hypernatraemia that can occur from excess sodium intake. Clinical examination is the key to this differentiation. It is then necessary to differentiate between simple dehydration and DI, bearing in mind that, in brain-injured patients, thirst is often an unreliable or absent symptom. Dehydration is associated with low urine volume (in the absence of renal failure), whereas DI results in high urine output, often in excess of 6 litre day$^{-1}$. Other causes of high urine volume should be excluded; in brain-injured patients, these include pre-hospital fluid resuscitation, osmotic diuretics, hypertonic saline, and the application of triple-H therapy (hyperglycaemia, hypertension, and haemodilution) to treat cerebral vasospasm.

In the context of brain injury, the diagnosis of DI is made in the presence of:

- (i) increased urine volume (usually $>3000$ ml per 24 h);
- (ii) high serum sodium ($>145$ mmol litre$^{-1}$);
- (iii) high serum osmolality ($>305$ mmol kg$^{-1}$);
- (iv) abnormally low urine osmolality ($<350$ mmol kg$^{-1}$).

While waiting for these laboratory tests, a simple, but not 100% reliable, bedside test of urine specific gravity (SG) may be of assistance. In the presence of high urine output and high serum sodium, urine SG $<1.005$ is suggestive of DI.

Measurement of plasma ADH concentration can distinguish between nephrogenic and central DI, but confirmation of the diagnosis ultimately comes with the observation of the response to synthetic ADH.

**Specific management**

There are two aims in the management of DI: replacement and retention of water and replacement of ADH. Conscious patients are able to increase their own water intake and this is often sufficient treatment if the DI is self-limiting. In unconscious patients, fluid replacement is achieved with water administered via a nasogastric tube or i.v. 5% dextrose. Excessive fluid input is a risk in unconscious patients and treatment should be guided by accurate assessment of volume status. If urine output continues $>250$ ml h$^{-1}$, synthetic ADH should be administered. This is usually in the form of small titrated doses of 1-deamino-8-D-arginine vasopressin which can be given intranasally (100–200 µg) or i.v. (0.4 µg). Small doses are preferred as they minimize the risk of over-prolonged action and can be titrated to obtain the desired clinical effect. $^3$

Over rapid correction of hypernatraemia can have serious side-effects such as pulmonary and cerebral oedema. In general terms, serum sodium should be reduced no quicker than 10 mmol litre$^{-1}$ day$^{-1}$, although more rapid correction is probably safe in those in whom the hypernatraemia developed over a period of only a few hours.
References

7. Cort JH. Cerebral salt wasting. Lancet 1954; 266: 752–4

Please see multiple choice questions 11–15