PERSPECTIVE

Hyponatraemia: common and commonly misunderstood

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Hyponatraemia is common and has many causes. Although often asymptomatic or associated with nonspecific symptoms, diagnosis and treatment are required as it can lead to cerebral problems if it becomes severe.

Hyponatraemia is common in patients who have myocardial dysfunction or chronic conditions such as hypertension, type 2 diabetes or obesity, and is often partly due to medications used to treat these conditions. It is generally defined as a plasma sodium level less than 135 mmol/L, and is considered severe when the level is below 120 mmol/L. This article uses a case to discuss the pathophysiology of hyponatraemia and to suggest a practical approach to management to relieve symptoms and prevent worsening of the condition and a potential emergency situation.

Pathophysiology of hyponatraemia

Case scenario

'In the last fortnight she's not been her usual self. She spends all day in a chair, doesn't seem interested in anything anymore and is forgetting things. I'm worried she's getting dementia or has had another stroke.'

George has brought his wife Natalie to see you. Natalie is 62 years old and sees you regularly, mostly about her type 2 diabetes and her hypertension, which she has had for 10 to 15 years. She's had several other health problems, including a stroke that affected her speech, the right side of her face and her right arm some seven years ago and from which she made a good recovery. She became depressed following the stroke, however, and she has joint pain in her knees and hips that bothers her in the winter. Her medications include:

- *metformin/glibenclamide 500 mg/5 mg twice daily*
- *valsartan/hydrochlorothiazide 160 mg/12.5 mg per day*
- *amiloride 5 mg per day*
- *citalopram 20 mg per day*
- *piroxicam 10 mg/day.*

Over the past 10 years, Natalie's weight has increased from 65 kg to 78 kg (height, 164 cm), as has her blood glucose level (her glycosylated haemoglobin [A_{1c}] one month earlier was 8.8%). When she started

Key points

- **Hyponatraemia is common in patients with myocardial dysfunction or chronic conditions such as hypertension, type 2 diabetes and obesity.**
- **Plasma sodium levels may be misleading because of laboratory errors, solute excess or the presence of substances that are not soluble in water.**
- **Generally, chronic hyponatraemia is asymptomatic or associated with nonspecific symptoms such as tiredness and cramps. Acute or severe hyponatraemia, however, may be associated with impaired consciousness, seizures and death.**
- **Investigations include repeating the sodium measurement, excluding spurious hyponatraemia and measuring urine electrolytes. Further investigations may be needed to define the underlying causes of water excess (either 'appropriate' or 'inappropriate' secretion of antidiuretic hormone) or sodium depletion (usually excess sodium loss).**
- **Management aims to correct any underlying clinical cause and to correct the hyponatraemia by increasing the urinary cation excretion (by increasing sodium and potassium intake), diluting the urine (by using loop diuretics) and maintaining or increasing urine output.**
- **More active intervention such as intravenous hypertonic saline and/or vasopressin agonists may be needed in patients with acute severe hyponatraemia; these patients should be closely monitored in an intensive care environment.**

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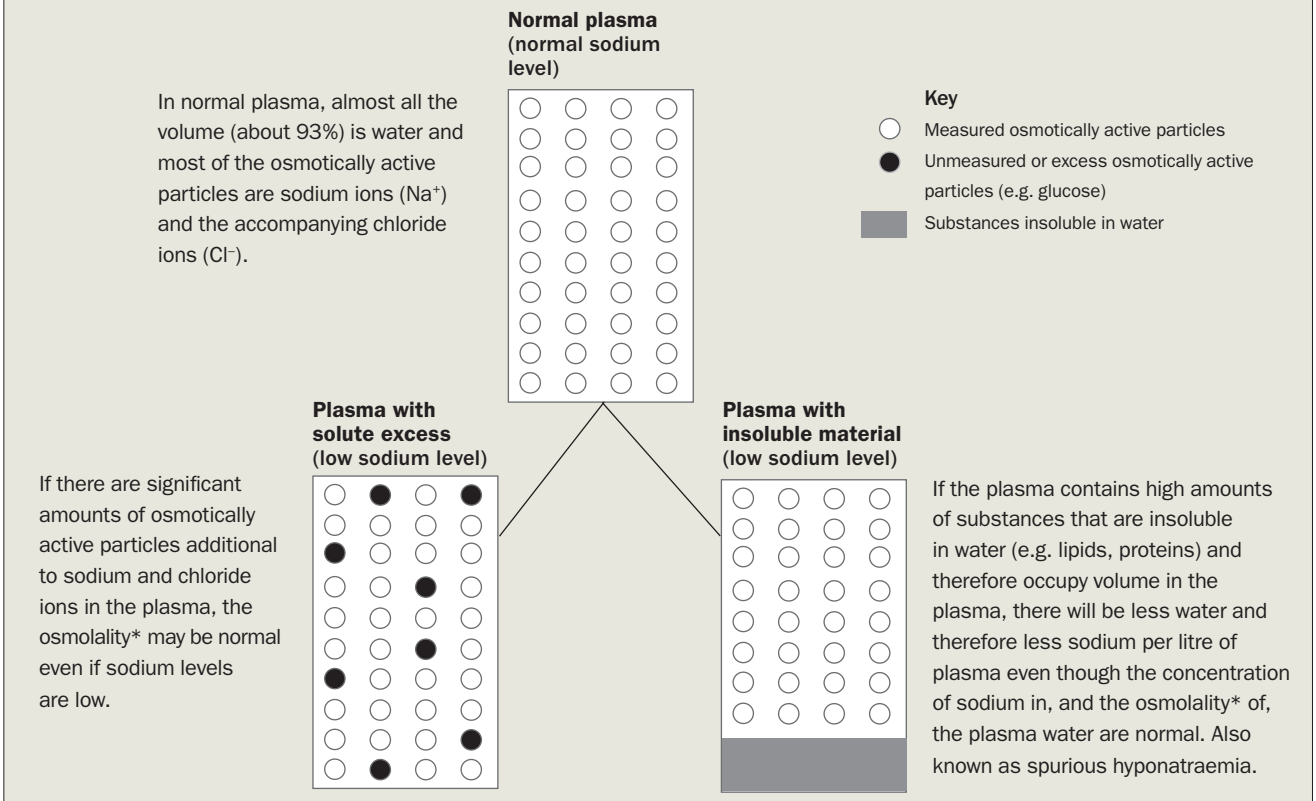
Causes of misleading measurements of plasma sodium



* Osmolality is a measure of the number of osmotically active particles per kg of solvent – i.e. in the plasma water, not in the whole plasma volume.

pioglitazone her feet and ankles swelled up 'like balloons' so she stopped it; she is reluctant to start insulin. Her blood pressure has been high (130 to 145/70 to 80 mmHg) but she has not been short of breath.

On examination, Natalie's Mini Mental State Examination score is 24/30 and she has some weakness of her right arm but no other neurological signs. She has minor pitting oedema in the lower half of her calves but her heart sounds are dual and her chest is clear. You arrange to check her general biochemistry and haematology and to see her again in two days' time.

The next morning you're surprised to find from the laboratory results that Natalie has hyponatraemia (plasma sodium, 124 mmol/L) because one month ago it was in the reference range at 134 mmol/L. You ring the laboratory to check the result is correct.

What could cause Natalie's sodium report to be misleading?

Apart from errors during the specimen collection process or in the testing laboratory, plasma sodium levels may be affected by the presence of an unmeasured solute (e.g. a sugar) or a nonaqueous material (e.g. lipids, proteins; see the box above). Theoretically, the presence of both a solute and a nonaqueous material could apply in Natalie's

Measurements of the concentration of osmotically active particles

Osmolarity

If the concentration of osmotically active particles is measured in the total plasma, the measurement is per litre of plasma and is called the osmolarity (milliosmoles per litre; mOsm/L). This measurement can be affected by the presence of materials not soluble in water (e.g. lipids or proteins). The calculation of the osmotically active particles in plasma from the measurements of the electrolytes, urea and glucose is based on their concentration per litre of plasma and is therefore the calculated osmolarity (mOsm/L).

Osmolality

If the concentration of osmotically active particles is measured in the plasma water (by an instrument called an osmometer), the measurement is called the osmolality (milliosmoles per kilogram of water; mOsm/kg). Measures of osmolality are not affected by the presence of substances not soluble in water.

In practice, there is very little difference between osmolality and osmolarity and the terms are often used interchangeably, although they refer to different units of measurement.

case – she may have high levels of plasma glucose (glucose is osmotically active) and/or triglyceride (which displaces plasma water; so-called 'spurious hyponatraemia').

One month ago, Natalie's average blood glucose level (BGL) calculated from her A_{1c} of 8.8% was 11.6 mmol/L (average BGL = 2 x A_{1c} – 6), and although she is likely to have abnormal triglyceride levels associated with her hyperglycaemia, they are unlikely to be high enough to cause significant hyponatraemia. In fact, her plasma glucose level measured on the same sample as the hyponatraemic one was 12.2 mmol/L and her plasma had not been noted to be turbid (a sign of high triglyceride levels). To exclude misleading results, the sodium assay can be repeated on a second blood sample. To exclude the presence of unmeasured solutes or nonaqueous materials, the osmolality (milliosmoles of solute per kilogram of solvent) of the plasma water in the sample can be measured (using an osmometer) and compared with the osmolarity (osmoles of solute per litre of solution) calculated from the sodium, potassium, urea and glucose concentrations of the plasma (see the box on page 28).

Investigation of hyponatraemia

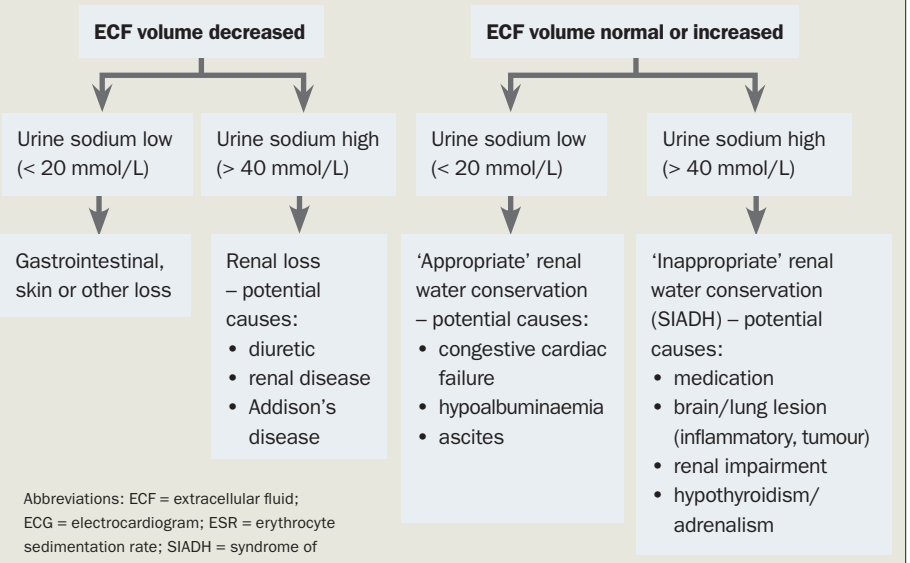
Investigative tests

- Confirm abnormality (ECG, thyroid function tests, biochemistry including liver function tests, albumin level, random cortisol level and markers of inflammation such as ESR and C-reactive protein)
- Measure plasma osmolality
- Clinically assess ECF volume
- Measure urine sodium level (note that diuretics may invalidate interpretation)

Interpretation of test results

Plasma osmolality normal: spurious hyponatraemia – see the boxes on page 28

Plasma osmolality decreased: consider causes based on ECF volume, as follows



Abbreviations: ECF = extracellular fluid; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

Are Natalie's symptoms likely to be caused by her hyponatraemia?

Chronic hyponatraemia, which Natalie has, is often asymptomatic or associated with nonspecific symptoms (forgetfulness, confusion, lethargy, fatigue and muscle cramps). Severe hyponatraemia (plasma sodium level below 120 mmol/L), however, can be associated with impaired consciousness, seizures, coma and death, particularly if it is acute.

The distribution of body water between extracellular and intracellular fluids (ECF and ICF) depends on the number of particles that are osmotically active in the two compartments – largely the cations and their accompanying anions: sodium in the ECF and potassium in the ICF. Urea, while osmotically active, is distributed throughout total body water and does not affect water distribution between ICF and ECF. Changes in the ECF sodium concentration will cause water to move between the ECF and ICF and change cell volumes, which could cause cerebral problems as the brain is in a confined anatomical space. Cellular enzymes and membrane excitability are affected by the osmolality and electrolyte concentration of body fluids.

What are the likely causes of Natalie's hyponatraemia?

ECF sodium levels decrease because of excess water content and sodium dilution and/or ECF sodium depletion. Water excess may be associated with 'appropriate' secretion of antidiuretic hormone (ADH) increasing reabsorption of renal water, given a physiological state when the renin–angiotensin–aldosterone system and ADH system are stimulated (by oedematous states, for example). Alternatively, there is the syndrome of 'inappropriate' ADH secretion (SIADH) despite a normal or expanded ECF volume (e.g. stimulated by some medications). Sodium depletion can theoretically occur because of inadequate intake but is usually caused by excess losses through the skin, gastrointestinal tract or kidneys. The causes of hyponatraemia are included in the box on this page, and common drugs causing SIADH are listed in the box on page 30.

Natalie's hyponatraemia may well have components of both water excess and sodium depletion, with her oedematous state suggesting water excess (and appropriate ADH secretion) and the presence of some of the conditions associated with SIADH (see the box above).

Common medications causing SIADH

- Psychotropics – especially tricyclic antidepressants, SSRIs, phenothiazines
- Anti-inflammatories – NSAIDs
- Antiepileptics – especially carbamazepine, barbiturates
- Sulfonylureas – especially glibenclamide
- ADH analogues – vasopressin, desmopressin overdose, oxytocin

Abbreviations: ADH = antidiuretic hormone; NSAID = nonsteroidal anti-inflammatory drug; SIADH = syndrome of inappropriate ADH secretion; SSRI = selective serotonin reuptake inhibition.

Table. Natalie's 24-hour urine and plasma chemistry results

	Test result	Normal range*
24-hour urine (volume, 1350 mL)		
Sodium	86 mmol/day	40 to 100 mmol/day
Potassium	72 mmol/day	50 to 140 mmol/day
Urea	240 mmol/day	170 to 580 mmol/day
Creatinine	5.3 mmol/day	8.8 to 23.0 mmol/day
Osmolality	402 mOsm/kg	–
Plasma		
Sodium	122 mmol/L	135 to 145 mmol/L
Potassium	3.4 mmol/L	3.5 to 4.9 mmol/L
Chloride	89 mmol/L	100 to 109 mmol/L
Bicarbonate	25 mmol/L	22 to 32 mmol/L
Urea	8.4 mmol/L	2.7 to 8.0 mmol/L
Creatinine	92 µmol/L	50 to 120 µmol/L
Osmolality	266 mOsm/kg	285 to 295 mOsm/kg

* NHMRC recommendation.

A practical approach to investigation

What investigations should you arrange and how would they help?

Potential causes of Natalie's hyponatraemia include worsening of her tendency towards oedema (e.g. unrecognised myocardial infarction, worsening cardiac function or hypoalbuminaemia) or inappropriate ADH secretion (e.g. covert hypothyroidism, occult malignancy/inflammation). ECG, thyroid function tests and biochemistry tests (including liver function tests and measurement of albumin level, random cortisol level and markers of inflammation such as ESR and C-reactive protein) are simple tests to perform.

Usually the urine sodium level will distinguish between sodium depletion (spot urine sodium level is low, below 20 mmol/L), reflecting activation of the renin–angiotensin–aldosterone system, and renal sodium retention. Water excess is associated with a normal or high urinary sodium level (spot urine sodium level above 40 mmol/L). However, Natalie's diuretic therapy will reduce her renal capacity to reabsorb sodium and, therefore, the usefulness of urine sodium estimation. Nonetheless, information about her 24-hour urine and plasma biochemistry will be useful in guiding therapy.

Natalie 'has not been her usual self' for two weeks, as her husband reported, and she is probably in a steady physiological state. Her excretion of solutes and water will mirror her daily intake. Measuring her plasma and 24-hour urine electrolytes will identify whether she is likely to improve or deteriorate and how she can be treated to increase her plasma sodium and osmolality.

If Natalie's 24-hour urine concentration of sodium plus potassium is greater than the sum of her plasma levels of these two electrolytes, she will effectively be retaining water free of these cations and her plasma sodium and osmolality levels will decrease further. If her urine sodium plus potassium concentration is less than their sum in her plasma, she will effectively be excreting cation-free water and her plasma sodium and osmolality levels will increase. The more dilute her urine and the more urine she produces, the larger the amount of free water she can excrete and the quicker her sodium and osmolality will increase.

Natalie's treatment should aim to decrease her water intake, increase her urinary cation concentration and maintain or increase her urine volume.

Case scenario continued

Natalie's ECG showed some nonspecific ST-segment and T-wave changes and some possible reduction in voltage in the anterior leads but no evidence of myocardial infarction. Her thyroid function test results, plasma albumin level, other biochemistry measurements and inflammatory markers were normal. Her 24-hour urine and plasma chemistry results are shown in the Table.

How do you interpret Natalie's test results?

The nonspecific changes on Natalie's ECG are consistent with her hyponatraemia (plasma sodium on the repeat sample, 122 mmol/L) and hyponatraemia is confirmed.

At 86 mmol/day, Natalie's 24-hour urine sodium excretion is within the normal range of 40 to 100 mmol/day. Her urinary cation concentration (sodium plus potassium [(86 + 72 mmol/day) ÷ 1.35 L = 117 mmol/L) is slightly less than her plasma cation concentration (122 + 3.4 = 125.4 mmol/L), suggesting that she is excreting some cation-free water and that her plasma sodium and osmolality will increase.

Frusemide's role in diluting urine concentration

The renal concentration gradient that allows the concentration/dilution of urine above/below the concentration of the plasma is established in the loop of Henle by countercurrent exchange between the ascending and descending loops. Sodium pumped from the ascending loop enters the descending loop and progressively increases the sodium concentration as the descending loop approaches the bottom of the loop of Henle. As the loop ascends, the removal of sodium progressively lowers the sodium concentration and osmolality from the maximum concentration at the bottom (e.g. 1200 mOsm/kg, roughly four times the concentration of plasma, 300 mOsm/kg) to the minimum concentration where the ascending loop joins the distal tubule (e.g. 100 mOsm/kg). The final dilution occurs in the so-called thick segment of the loop of Henle.

The thick segment is affected by loop diuretics such as frusemide but not by thiazide diuretics such as hydrochlorothiazide. By reducing sodium reabsorption from the ascending loop, frusemide decreases the effectiveness of the loop of Henle in concentrating/diluting the urine as sodium is not transferred from the thick ascending loop to the descending loop. This reduces the concentration in the descending loop and decreases the dilution in the ascending loop.

Natalie's creatinine clearance is 40 mL/min, suggesting moderate impairment of renal function [(urinary creatinine mmol/day ÷ plasma creatinine μmol/L) ÷ 1440; (5.3 ÷ 92) ÷ 1440 = 40 mL/min].

Given Natalie's age, diuretic therapy and renal impairment, her urinary sodium concentration is relatively low and may reflect activation of the renin–angiotensin–aldosterone system (secondary hyperaldosteronism), which would be accompanied by 'appropriate' ADH secretion activating renal water reabsorption and retention.

A practical approach to treatment

Case scenario continued

Natalie is transferred to hospital and admitted to the high dependency unit.

How can Natalie's hyponatraemia be corrected?

Natalie is taking several medications that could be contributing to her hyponatraemia: her diuretics (thiazide and amiloride) and her SSRI (citalopram) and her NSAID (piroxicam).

The diuretics could be stopped and thiazide replaced with a loop diuretic such as frusemide (20 or 40 mg/day), which will maintain urine volume and reduce urine concentration (see the box on this page). Instead of amiloride, potassium chloride could be given, which would increase urinary potassium excretion and replete intracellular potassium, shifting water from the extracellular to the intracellular compartment.

The NSAID could be stopped and replaced with paracetamol, and the SSRI could be phased out over the next seven days.

Hyponatraemia: practice points

- Plasma sodium levels may be misleading because of laboratory errors, solute excess or the presence of substances that are not soluble in water.
- Solute excess in the ECF compared with the ICF causes water to move from the ICF to the ECF, diluting plasma sodium. The sodium concentration decreases by approximately one-third of the ECF excess solute concentration above normal.
- The presence of plasma substances that are not soluble in water but occupy plasma volume (such as lipids and proteins) will reduce the amount and concentration of sodium per litre of plasma volume (i.e. reduce the osmolarity). In these cases, the measured osmolality in the water will be higher than the calculated osmolarity in total plasma.
- Generally, chronic hyponatraemia (plasma sodium between 120 mmol/L and 135 mmol/L) is asymptomatic or associated with nonspecific symptoms such as tiredness and cramps, but acute or severe hyponatraemia (plasma sodium below 120 mmol/L) may be associated with impaired consciousness, seizures and death.
- Hyponatraemia occurs because of excess water or decreased sodium in the ECF. These are distinguished clinically by signs of decreased (sodium depletion), normal or increased (water excess) ECF volume.
- Investigations include repeating the sodium measurement, excluding spurious hyponatraemia and measuring urine electrolytes. Further investigations may be needed to define the underlying causes of sodium depletion (usually excess sodium loss) or water excess (either 'appropriate' or 'inappropriate' secretion of ADH).
- Management aims to correct any underlying clinical cause and to correct the hyponatraemia by increasing the urinary cation excretion (by adding sodium and potassium), diluting the urine (by using loop diuretics) and maintaining or increasing urine output.
- More active intervention such as intravenous hypertonic saline and/or vasopressin agonists may be needed in patients with acute severe hyponatraemia; these patients should be closely monitored in an intensive care environment.
- Plasma sodium levels should not be increased by more than 18 mmol/L in any 48-hour period to avoid the risk of a cerebral disequilibrium syndrome.

Abbreviations: ADH = antidiuretic hormone; ECF = extracellular fluid; ICF = intracellular fluid.

Natalie's water intake could be reduced (e.g. to 800 mL/day) with limited intake of high water foods such as melon and oranges. Theoretically, extra sodium could be given orally (as salt tablets) or intravenously (as hypertonic saline) but given her peripheral oedema and probable left ventricular dysfunction, this would be considered only if the other measures do not sufficiently increase plasma sodium.

The combination of a more dilute urine and increased sodium excretion (from the frusemide), increased urinary potassium excretion

(from potassium supplementation), lesser effects of her NSAID and SSRI on ADH, and water restriction will increase Natalie's cation-free water excretion and her plasma sodium level. Natalie's plasma and urine chemistry can be monitored to assess the effectiveness of the various interventions.

How quickly should Natalie's hyponatraemia be corrected?

As noted earlier, a decreased ECF sodium concentration will result in water movement from the ECF to the ICF, changing the cell volume and potentially causing cerebral problems. Over the longer term (several days), cells have the capacity to regulate their total effective osmolal contents by generating or removing osmotically active metabolites.[1,2] They can thus restore normal cell volume and equalise ICF with ECF osmolality. In Natalie's case, this is likely to have occurred. If her hyponatraemia were to be rapidly reversed then the increase in the plasma sodium concentration would result in shifts of ICF water to the ECF, decreasing cell volume and potentially causing CNS problems.

Natalie's hyponatraemia is associated with symptoms, could worsen and should be corrected. However, the plasma sodium level should not increase by more than 18 mmol/L in 48 hours to allow time for cells to generate osmotically active metabolites and maintain equality of intracellular and extracellular osmolality without water shifting from the ICF to the ECF.[3,4] Natalie's plasma chemistry should be checked at least second-daily to ensure that therapy is effective, but not too effective, in increasing plasma sodium.

In severe cases associated with acute neurological signs, more active intervention such as intravenous hypertonic saline and/or vasopressin antagonists (the 'aptans') are given as these can rapidly increase plasma sodium levels. In these cases, even closer monitoring should occur, preferably in an intensive care environment.

Conclusion

A common condition in patients with myocardial dysfunction or chronic conditions such as hypertension, type 2 diabetes and obesity, chronic hyponatraemia is generally asymptomatic. Acute or severe hyponatraemia (plasma sodium level below 120 mmol/L), however, may be associated with impaired consciousness, seizures and death. The plasma sodium level itself may be misleading because of laboratory error, solute excess or the presence of substances that are not soluble in water; investigations include repeating the sodium measurement, excluding spurious hyponatraemia and measuring urine electrolytes. Further investigations may be needed to define the underlying causes of water excess (either 'appropriate' or 'inappropriate' secretion of ADH) or sodium depletion (usually excess sodium loss). Management is directed towards correcting any underlying clinical cause and increasing the urinary cation excretion (by adding sodium and potassium), diluting the urine (by using loop diuretics) and maintaining or increasing urine output. More active intervention such as intravenous hypertonic saline and/or vasopressin agonists may be needed in cases of acute severe hyponatraemia, which should be managed in an intensive care environment. Practice points regarding hyponatraemia are given in the box on page 31. **CT**

References

1. Mount DB. The brain in hyponatremia: both culprit and victim. Semin Nephrol 2009; 29: 196-215.
2. Sterns RH, Silver SM. Brain volume regulation in response to hypo-osmolality and its correction. Am J Med 2006; 199 (7 Suppl 1): S12-S16.
3. Sterns RH. Severe symptomatic hyponatremia: treatment and outcome. A study of 64 cases. Ann Intern Med 1987; 107: 656-664.
4. Sterns RH, Cappuccio JD, Silver SM, Cohen EP. Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. J Am Soc Nephrol 1994; 4: 1522-1530.

Further reading

Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med 2000; 342: 1581-1589.

Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. N Engl J Med 2007; 356: 2064-2072.

Reynolds RM, Padfield PL, Seckl JR. Disorders of sodium balance. BMJ 2006; 332: 702-705.

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