Management of hyponatraemia

Introduction

Hyponatraemia (serum sodium level <135 mmol/litre) is the most common electrolyte abnormality among hospitalized patients. A prevalence rate as high as 15–30% has been reported among patients admitted to acute and intensive care units (Hoorn et al, 2004; Jaber et al, 2006). Evidence suggests an increase in mortality associated with even a mild degree of hyponatraemia (Waikar et al, 2009). Besides its significance as a potential cause of morbidity and mortality, hyponatraemia could also serve as a useful indicator for undiagnosed underlying pathology such as endocrine disorders or malignancy.

A systematic approach towards the clinical assessment and interpretation of biochemical abnormalities is vital to facilitate the diagnosis and management of hyponatraemia. The optimal treatment of hyponatraemia should take into account its severity, duration and mode of clinical presentation. Overzealous correction could result in irreversible neurological complications.

Pathophysiology

Understanding the normal physiological mechanisms for maintaining eunatraemia (serum sodium 135–145 mmol/litre) is crucial for correctly identifying the cause of hyponatraemia. Serum sodium level and osmolality are both normally tightly regulated by three major mechanisms: thirst, antidiuretic hormone and the angiotensin–renin system. An increase in serum osmolality stimulates the hypothalamic osmoreceptors resulting in the thirst sensation as well as promoting secretion of antidiuretic hormone from the neurohypophysis. Antidiuretic hormone release can also occur in response to volume depletion through activation of the baroreceptors in the carotid sinus. Activation of the renin–angiotensin system in response to volume depletion promotes release of aldosterone which regulates serum sodium level by increasing its reabsorption in exchange for potassium in the distal tubule. Most causes of spontaneous (non-iatrogenic) hyponatraemia can be traced back to a defect in one or more of the above mechanisms.

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Causes of hyponatraemia

The most important step in diagnosing the cause of hyponatraemia is assessing the volume status of the patient. The causes of hyponatraemia can be classified into three categories based on the volume status of the patient: hypovolaemic, euvolaemic and hypervolaemic (*Figure 1*). Hypovolaemic hyponatraemia is characterized by depletion of both total body sodium and water while euvolaemic hyponatraemia is characterized by normal total body sodium and normal or increased total body water. Hypervolaemic hyponatraemia involves both increased total body water and sodium levels.

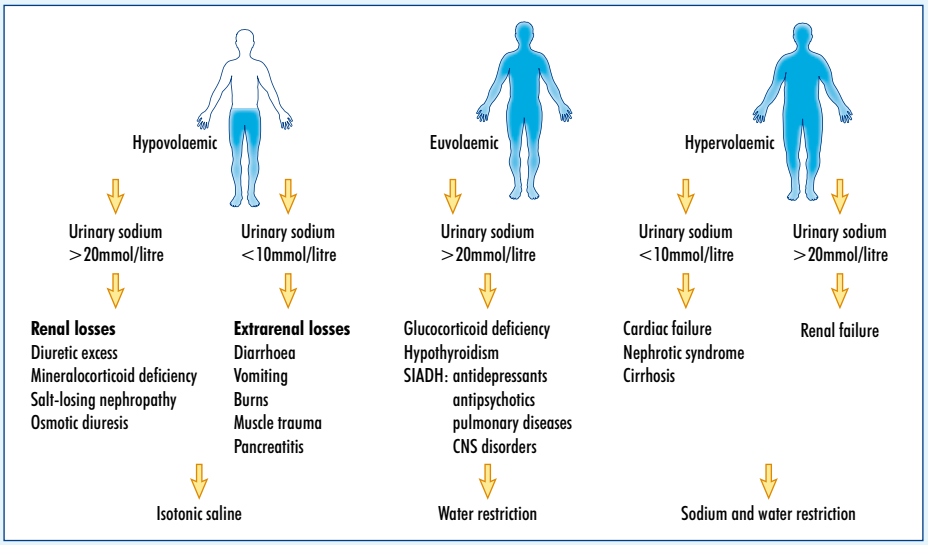
Hypovolaemic hyponatraemia is caused by excess loss of sodium from the kidneys (diuretics, osmotic diuresis and aldosterone deficiency) or by non-renal losses such as from the gastrointestinal tract (vomiting and diarrhoea), the skin (excessive sweating or burns) or third space loss (surgical cases such as small bowel obstruction and pancreatitis). The distinction between renal and non-renal loss of sodium could be obvious from the history but measurement of urinary sodium excretion may further simplify differentiation (>20 mmol/litre in renal causes). The fractional excretion of sodium (FENa), defined as the percentage of sodium filtered by the kidney which is excreted in the urine, is a more reliable measure to differentiate renal from non-renal sodium loss than urinary sodium concentration alone. It is calculated by the formula:

$$\text{FENa} = 100\text{x} \frac{\text{urinary sodium x serum creatinine}}{\text{serum sodium x urinary creatinine}}$$

A low FENa (<1%) indicates the presence of a hypovolaemic stimulus to the kidneys to conserve sodium (non-renal loss) while confirming satisfactory renal tubular resorptive function. A high FENa (>3%) indicates sodium wasting secondary to an intrinsic renal pathology or cerebral salt wasting. The use of diuretics increases the FENa and this should be ruled out to avoid misdiagnosis of the cause of hyponatraemia.

Euvolaemic hyponatraemia is by and large secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) but other causes such as psychogenic polydipsia, glucocorticoid deficiency and hypothyroidism should also be considered. The causes and criteria for diagnosis of SIADH are discussed separately.

Figure 1. Classification of causes of hyponatraemia. SIADH = syndrome of inappropriate antidiuretic hormone secretion.



Hypervolaemic hyponatraemia is encountered in volume overload states such as congestive cardiac failure, nephrotic syndrome, chronic renal failure and cirrhosis.

Symptoms of hyponatraemia

The nature and severity of symptoms of hyponatraemia depends on the level of hyponatraemia and the rate at which the serum sodium level dropped below the normal range. Common symptoms reported with mild to moderate hyponatraemia (serum sodium <135 mmol/litre and <130 mmol/litre respectively) include headache, lethargy, anorexia, nausea, dysguesia, muscle cramps, drowsiness and confusion. Severe hyponatraemia can result in hallucination, seizures, coma, respiratory arrest and death (Adrogue and Madias, 2000).

Patients with acute hyponatraemia are more prone to develop profound symptoms and cerebral oedema. In contrast, patients with chronic hyponatraemia have less pronounced symptoms because of adaptive mechanisms in the brain that mitigate the degree of cerebral oedema. The normal brain tissue adapts to hyponatraemia via extrusion of sodium and organic osmolytes to the extracellular compartment to prevent cellular oedema. However, this protective adaptive mechanism usually takes several hours to begin which accounts for the severity of symptoms of acute hyponatraemia and the associated risk of cerebral oedema (Strange, 1992; Adrogue and Madias, 2000).

Clinical assessment

A meticulous clinical assessment is necessary to identify the severity, duration and cause of hyponatraemia. The history should focus on the nature and duration of hyponatraemic symptoms, symptoms of extra-renal loss of body fluid such as vomiting and diarrhoea, the presence of underlying pathology such as endocrinopathy, infection and malignancy as well as drug history such as the use of diuretics or medications which could cause SIADH.

A thorough physical examination to assess the volume status of the patient including assessing skin turgidity, tachycardia and postural hypotension helps to identify the cause of hyponatraemia as well as dictating further investigation and management. The presence of oedema, which is often caused by both salt and water retention, indicates a hypervolaemic state. SIADH is not associated with oedema since water retention is not accompanied by salt reabsorption and there is no significant increase in extracellular fluid volume because of the hyposmolality-mediated shift of water into the intracellular compartment.

Searching for stigmata of endocrine disorders such as Addison's disease, hypothyroidism and hypopituitarism could prove useful as hyponatraemia can be the initial manifestation of these treatable but potentially life-threatening conditions. Both early and advanced malignancy can also present with hyponatraemia secondary to SIADH.

Investigations

A basic biochemical profile including electrolytes, urea, calcium, glucose, renal and liver function is a useful starting point. Euvolaemic hyponatraemic patients should also have measurement of paired serum and urine osmolalities, urine sodium level, thyroid function and a 9.00am cortisol level which are all part of the necessary criteria to diagnose SIADH. Further investigations may be needed such as short synacthen and/or full pituitary function profile in the cortisol-deficient patient, chest X-ray and computed tomography scan of the thorax and abdomen in patients with SIADH for which no apparent cause has been identified, or computed tomography scan or magnetic resonance imaging scan of the brain in those suspected to have an underlying intracranial pathology.

Pseudohyponatraemia

Pseudohyponatraemia should be considered in the differential diagnosis of euvolaemic hyponatraemia. It is often caused by a disproportionate increase in the non-aqueous components of plasma such as lipids (hyperlipidaemia) and proteins (multiple myeloma). This results in a decrease in the aqueous component of plasma without any change in the physiologically important concentration of sodium per unit volume of water. Pseudohyponatraemia should be suspected in patients with euvolaemic normosmolar hyponatraemia and history of multiple myeloma, recent immunoglobulin therapy or marked hyperlipidaemia. This can be differentiated from true hyponatraemia by direct ion-selective photometry which specifically measures the physiologically relevant aqueous component of plasma.

Another common cause of spurious hyponatraemia is inappropriate blood sample collection from a venous site in the immediate vicinity of an intravenous infusion. The unexpected finding of an acutely low serum sodium level which does not correlate with the patient's clinical status should be verified with repeat measurement of the serum sodium level before it triggers unnecessary investigation and treatment.

Hyperglycaemia-associated hyponatraemia

Hyperglycaemia has a variable effect on plasma sodium level. It causes an increase in serum osmolality which promotes a shift of water from cells thereby causing dilutional hyponatraemia. The plasma sodium level is estimated to fall by 1 mmol/litre for every 3.5 mmol/litre rise in plasma glucose level above the normal range. Hyperglycaemia also causes osmotic diuresis which often involves a greater rate of urinary water loss than urinary sodium loss. This excess water loss from osmotic diuresis could raise plasma sodium level and osmolality thereby counteracting the direct dilutional effect of hyperglycaemia on plasma sodium.

Treatment of hyponatraemia

The treatment of hyponatraemia should take into account different factors such as its cause, severity and duration, the clinical status of the patient and the presence of comorbidities such as heart failure which could dictate the rate of fluid replacement. The temptation to rapidly correct hyponatraemia should be resisted to prevent the potentially catastrophic, often irreversible neurological complication of central pontine myelinolysis. This is particularly true for cases of chronic hyponatraemia where the brain tissue has already taken adaptive measures to mitigate cerebral oedema. The aim of treatment should be to achieve a slow and steady increase in serum sodium level at a rate not exceeding 0.5 mmol/hr (Greenberg et al, 2007). The volume status of the patient, hourly measurement of input-output and serial measurement of serum sodium level are all useful parameters to monitor response to treatment.

The treatment of hypovolaemic hyponatraemia is fluid replacement with isotonic saline guided by physiological parameters such as heart rate, blood pressure and urine output. The euvolaemic patient with mild

to moderate hyponatraemia can be treated by addressing the underlying cause (e.g. withdrawing offending drugs, treating infections) as well as fluid restriction. The actual volume of fluid restriction is determined by the desired rate of improvement in serum sodium level and the expected compliance of the patient but in most cases fluid restriction of 50–60% of the normal fluid intake or <800 ml/24 hr is sufficient to create a negative water balance and restore eunatraemia (Gross, 2001; Greenberg et al, 2007). The level of fluid restriction can be further escalated if necessary depending on the biochemical and clinical response of the patient.

The use of antidiuretic hormone antagonist drugs such as demeclocycline is recommended in mild to moderate hyponatraemia refractory to fluid restriction or in cases of severe hyponatraemia alongside fluid restriction. Vasopressin-2 receptor antagonists such as tolvaptan are also effective in treating both euvolaemic and hypervolaemic hyponatraemia although their relatively high cost currently precludes their routine use (Czerwiec et al, 2006; Berl et al, 2010). Hypertonic (3%) saline is usually reserved for use in acute severe hyponatraemia with neurological manifestations such as seizure, drowsiness and coma. This treatment should ideally be supervised by a specialist in an intensive care setup.

Central pontine myelinolysis (osmotic demyelination syndrome)

Acute hyponatraemia (<48 hours duration) can be complicated by cerebral oedema which can manifest with confusion, seizures and coma. This is the result of osmotic gradient-mediated movement of water into the brain cells. The brain can adapt to cellular oedema over 2–3 days by promoting extrusion of sodium, potassium and organic osmolytes to the extracellular space (Chan et al, 1991; Strange, 1992).

Rapid correction of hyponatraemia once the brain's adaptive mechanism against cerebral oedema has taken place could cause shrinkage of brain cells and the syndrome of osmotic demyelination also known as cerebral pontine myelinolysis, although the condition can involve other areas of the brain besides the pons (Chan et al, 1991; Laureno and Karp, 1993; Cappuccio et al, 1994). The condition manifests with symptoms of dysarthria, dysphagia, paraparesis, quadriparesis, seizures and coma. The demyelination lesions can be detected on computed tomography and magnetic resonance imaging brain scans but the absence of radiological signs does not rule out the diagnosis as it can take up to 4 weeks for signs to evolve (Brunner et al, 1990).

This neurological complication is often irreversible but some manifestations can improve with time and supportive therapy. Reports from animal models and case histories have indicated some response to relowering of serum sodium with desmopressin (Grieff et al, 2008). The best approach remains prevention of this debilitating neurological complication through careful monitoring of the rate of correction of hyponatraemia. The recommended rate for the correction of hyponatraemia is 0.5 mmol/litre/hour or not more than 12 mmol/litre in the first 24 hours.

Table 1. Causes of syndrome of inappropriate antidiuretic hormone secretion

Malignancy	Carcinoma	Lung
		Oropharynx
		Gastrointestinal tract
		Genitourinary tract
	Lymphoma	
Pulmonary disorders	Infections	Pneumonia
		Tuberculosis
	Positive pressure ventilation	
	Asthma	
Drugs	Psychotropic	Selective serotonin-reuptake inhibitors
		Tricyclics
		Antipsychotics
	Carbamazepine	
	Clofibrate	
	MDMA (Ecstasy)	
	Narcotics	
	Non-steroidal anti-inflammatory drugs	
	Cyclophosphamide	
CNS disorders	Infections	Meningitis
		Encephalitis
		Acquired immune deficiency syndrome
	Intracranial bleeding	
	Cerebrovascular accident	
	Brain tumour	
	Head trauma	

Syndrome of inappropriate antidiuretic hormone secretion

SIADH is the most common cause of euvolaemic hyponatraemia. It is caused by non-osmotic dependent release of antidiuretic hormone which results in inappropriate water retention in the face of low serum osmolality and sodium level. Several clinical entities cause SIADH. The most commonly encountered causes include pulmonary and CNS diseases (infections, neoplasms, haemorrhage), other neoplasms, drugs with psychotropic effects such as antidepressants and antipsychotics, narcotics and chemotherapeutic agents (*Table 1*).

Diagnosis of SIADH requires the presence of hyponatraemia and inappropriately concentrated urine in the face of low effective serum osmolality (*Table 2*).

There are important caveats to the biochemical criteria for the diagnosis of SIADH. Glucocorticoid deficiency and hypothyroidism should be ruled out since both conditions can result in a biochemical profile indistinguishable from SIADH. Clinical euvolaemia is also an essential criterion to fulfil before diagnosing SIADH since volume depletion is also a potent stimulus for the release of antidiuretic hormone (Berl and Ellison, 2007). This is particularly true in cerebral salt wasting which is difficult to distinguish from SIADH on biochemical criteria alone. Erroneous diagnosis of SIADH in the volume-depleted hyponatraemic patient could result in inappropriate treatment with fluid

Table 2. Criteria for diagnosis of syndrome of inappropriate antidiuretic hormone secretion

Essential features of syndrome of inappropriate antidiuretic hormone secretion
Decreased effective osmolarity: <275 mOsm/kg of water
Urinary osmolarity >100 mOsm/kg of water
Urinary sodium >40 mmol/litre with normal dietary salt intake
Normal thyroid and adrenal function
Clinical euvolaemia
No recent use of diuretic agents

restriction causing further worsening of clinical status (Cerdà-Esteve et al, 2008).

Cerebral salt wasting syndrome

Cerebral salt wasting syndrome is characterized by hyponatraemia and extracellular volume depletion. It is often confused with SIADH because it has essentially similar biochemical features. This is particularly true when the clinical signs of extracellular volume depletion are subtle. However, the distinction from SIADH is crucial as fluid restriction exacerbates the volume depletion and the clinical status of the patient.

Cerebral salt wasting syndrome is often encountered in patients with subarachnoid haemorrhage but it can also occur in association with CNS tumours, infections and following neurosurgical procedures. There are two major proposed mechanisms to explain the renal loss of sodium in cerebral salt wasting syndrome. Impaired sympathetic input at the level of the proximal tubule leading to sodium and urate loss as well as diminished renin release is one potential mechanism which could explain salt wasting. The other is the release of brain natriuretic protein from injured brain tissue which could also result in impaired sodium reabsorption and renin release (Cerdà-Esteve et al, 2008).

The biochemical profile encountered in cerebral salt wasting syndrome is difficult to distinguish from SIADH (Palmer, 2000, 2003; Cerdà-Esteve et al, 2008). Useful clues include urine sodium level >40 mmol/litre, urine osmolality >300 mosm/kg and low serum uric acid level owing to increased renal loss. The diagnosis, however, relies on accurate detection of signs of volume depletion such as decreased skin turgor, dry mucus membranes, tachycardia and hypotension. The treatment of cerebral salt wasting syndrome is fluid replacement with isotonic saline while closely monitoring volume status and biochemical profile.

Exercise-associated hyponatraemia

This is defined as hyponatraemia occurring during the first 24 hours following prolonged physical activity such as participation in endurance events. This has become increasingly common because of a trend towards non-thirst-driven copious fluid intake. An incidence as high as 13% has been reported among participants in endurance events (Almond et al, 2005). The mechanism of exercise-associated hyponatraemia involves exercise-induced antidiuretic hormone release coupled with high fluid intake and loss of sodium through excessive sweating (Almond et al, 2005; Clement et al, 2007; Ayus et al, 2008).

The presenting symptoms can be mild such as headache, nausea and dizziness but severe symptoms including drowsiness, collapse and seizures can also occur. Fatal cases of exercise-associated hyponatraemia have been reported (Clement et al, 2007). The mainstay of treatment in mild to moderate exercise-associated hyponatraemia is fluid restriction to allow spontaneous aquaresis and restoration of eunatraemia but severe hyponatraemia and presentation with neurological symptoms warrants treatment with hypertonic (3%) saline. The best approach to prevent this potentially serious cause of morbidity is avoiding excessive fluid intake during period of prolonged physical activity and using the physiological stimulus of thirst as a guide to fluid intake.

Conclusions

Hyponatraemia is a common electrolyte disorder among hospitalized patients. It is associated with significant morbidity even when the level of hyponatraemia is mild. A systematic approach towards its diagnosis and investigation allows appropriate management with optimal ou tcome. Correction should be undertaken with caution to avert neurological complications. BJHM

Conflict of interest: none.

Adrogue HJ, Madias NE (2000) Hyponatremia. *N Engl J Med* **342:** 1581–9

Almond CS, Fortescue EB, Shin AY et al (2005) Hyponatremia among runners in the Boston Marathon. *N Engl J Med* **352**(15): 1550–6

Ayus JC, Hew-Butler T, Kipps C et al (2008) Statement of the Second International Exercise-Associated Hyponatremia Consensus Development Conference, New Zealand, 2007. *Clin J Sport Med* **18:** 111

Berl T, Ellison DH (2007) The syndrome of inappropriate antidiuresis. *N Engl J Med* **356:** 2064–72

Berl T, Quittnat-Pelletier F, Verbalis JG et al (2010) Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol* **21**(4): 705–12

Brunner JE, Elias SB, Haggar AM, Kruger DF, Redmond JM (1990) Central pontine myelinolysis and pontine lesions after rapid correction of hyponatremia: a prospective magnetic resonance imaging study. *Ann Neurol* **27**(1): 61–6

Cappuccio JD, Cohen EP, Silver SM, Sterns RH (1994) Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. *J Am Soc Nephrol* **4**(8): 1522–30

Cerdà-Esteve M, Chillaron JJ, Cuadrado-Godia E et al (2008) Cerebral salt wasting syndrome: review. *Eur J Intern Med* **19**(4): 249–54

Chan L, Lien YH, Shapiro JI (1991) Study of brain electrolytes and organic osmolytes during correction of chronic hyponatremia. Implications for the pathogenesis of central pontine myelinolysis. *J Clin Invest* **88**(1): 303–9

Clement S, Siegel AJ, Verbalis JG et al (2007) Hyponatremia in marathon runners due to inappropriate arginine vasopressin secretion. *Am J Med* **120**(5): 461.e11–17

Czerwiec FS, Berl T, Gross P et al (2006) Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med* **355**(20): 2099–112

Greenberg A, Goldsmith SR, Schrier RW, Sterns RH, Verbalis JG (2007) Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med* **120**(11 Suppl 1): S1–21

Grieff M, Hix J, Kouides R et al (2008) DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. *Clin J Am Soc Nephrol* **3**(2): 331–6

Gross P (2001) Treatment of severe hyponatremia. *Kidney Int* **60:** 2417

Hoorn E, Lindemans J, Zietse R (2004) Hyponatremia in hospitalized patients; epidemiology, etiology and symptomatology. *J Am Soc Nephrol* **15:** 561(A)

Jaber BL, Madias NE, Upadhyay A (2006) Incidence and prevalence of hyponatremia. *Am J Med* **119**(Suppl 1): S30–5

Laureno R, Karp BI (1993) Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. *Medicine* **72**(6): 359–73

Palmer BF (2000) Hyponatraemia in a neurosurgical patient: Syndrome of inappropriate antidiuretic hormone secretion versus cerebral salt wasting. *Nephrol Dial Transplant* **15:** 262

Palmer BF (2003) Hyponatremia in patients with central nervous system disease: SIADH versus CSW. *Trends Endocrinol Metab* **14**(4): 182–7

Strange K (1992) Regulation of solute and water balance and cell volume in the central nervous system. *J Am Soc Nephrol* **3**(1): 12–27

Waikar SS, Mount DB, Curhan GC (2009) Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med* **122**(9): 857–65

KEY POINTS

- Hyponatraemia is the most common electrolyte disorder among hospitalized patients, and even mild hyponatraemia can cause significant morbidity.
- The presence of hyponatraemia can be a valuable clue to an undiagnosed underlying pathology.
- Accurate assessment of volume status facilitates correct diagnosis and treatment of the cause of hyponatraemia.
- The mode of clinical presentation of hyponatraemia depends on both its severity and duration.
- Management of chronic hyponatraemia requires close monitoring to avoid rapid correction which could result in irreversible neurological sequelae.