

Problem based review: The patient presenting with hyponatraemia.

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Abstract

Hyponatraemia is the most common electrolyte anomaly and is associated with significant morbidity and mortality. Patients with severe hyponatraemia often present to acute medical units with non-specific symptoms which can progress to overt neurological manifestations. There are many causes of hyponatraemia, the most common being drug-induced causes, particularly thiazide diuretics, and the Syndrome of Inappropriate ADH Secretion (SIADH). Initial assessment should include a careful evaluation of the patient's volume status, which helps to identify the most likely cause. This article utilises a recent case which presented to our AMU to illustrate the importance of a careful and systematic assessment of patients presenting to hospital with hyponatraemia. The new vasopressin receptor antagonists are explored as an option for the management of severe hyponatraemia.

Keywords:

Hyponatraemia, diuretic abuse, SIADH, vague symptoms, vaptans

Learning Points

- Investigating the cause of hyponatraemia in the absence of clear co-morbidities requires measurement of serum and urine osmolalities and urinary sodium
- Not all cases of inexplicable hyponatraemia are due to SIADH, and a urinary diuretic screen may be worthwhile if diagnostic criteria are not met
- Psychiatric illness in patients with hyponatraemia should provoke a high index of suspicion for self-inflicted hyponatraemia, either by water intoxication or diuretic abuse
- Steady restoration of sodium concentration (not more than 6mmol/l in 12 hours) is imperative so as to avoid unsustainable fluid shifts in the brain leading to central pontine myelinolysis and subsequent irreversible neurological deficits

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How common is hyponatraemia and how is it classified?

Hyponatraemia is probably the commonest of all electrolyte derangements. Some studies report an incidence of 0.97 % and a prevalence of approximately 2.48%.¹ A recent UK study reported prevalence rates as high as 15–30% in acute settings such as ITU and AMU.² There does not appear to be a sex or race predilection for hyponatraemia, although infants and the elderly are at greater risk.

Hyponatraemia was first described in medical literature in 1935 by Helwig et al., when it was believed that acute hyponatraemia could cause death or permanent brain damage by cerebral oedema.³ Few case studies were published at the time. Only in 1986 did Arieff et al. discover that 15 previously healthy young women had suffered permanent or fatal brain injury as a result of excessive administration of hypotonic fluids post-operatively.⁴

Today, hyponatraemia is encountered regularly on routine renal profile checking. Classification of patients according to concurrent fluid status (hyper-, hypo- or euvolaemic) is imperative to enable the identification of the most likely cause and to guide treatment.

- **Hypervolaemic hyponatraemia** is observed when there is a greater increase in water relative to that of sodium, although the amount of both solute and solvent is increased.

- **Hypovolaemic hyponatraemia** results from water and sodium loss; the amount of sodium lost is *relatively* greater than the amount of water lost.
- **Euvolaemic hyponatraemia** entails an increase in body water content for the same amount of sodium, thereby producing a dilutional effect.

These classifications alongside expected physical signs and some of the common causes for each category are shown in table 1.

Case vignette

A 65 year old Caucasian woman presented to the Acute Medical Unit (AMU) with five weeks of progressive tiredness, anorexia, anxiety and dyspnoea. A collateral history from her daughter confirmed that she had been non-specifically unwell for the past few weeks. She had a past medical history of Chronic Obstructive Pulmonary Disease (COPD), hypertension, generalised anxiety disorder and bipolar affective disorder, for which she was taking salbutamol and beclomethasone inhalers, amlodipine, zopiclone and olanzapine. She had no known drug allergies. The patient was a smoker of 20 cigarettes a day and consumed alcohol in moderation. She lived with her daughter and was independent in her mobility and activities of daily living.

On examination, the patient appeared anxious, although her vital signs were normal. She was alert and orientated. She was noted to be clinically dehydrated with pale, dry skin and

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Table 1. Classification by cause of hyponatraemia¹⁰

	Clinical Characteristics	Causes	
		Urine sodium < 30mmol/l	Urine sodium > 30mmol/l
Hypovolaemic	Tachycardia, postural Hypotension, dry skin, reduced skin turgor, raised blood urea, raised plasma renin	Vomiting Diarrhoea Burns Heat exposure (sweating)	Diuretics Addison's disease CSWS Salt-losing nephropathy
Euvolaemic	Blood urea normal or slightly reduced	Hypothyroid Any cause + hypotonic fluid	SIADH ACTH deficiency
Hypervolaemic	Peripheral, sacral, pulmonary oedema Ascites Raised JVP or CVP	Nephrotic syndrome Cardiac failure Liver failure	Renal failure Cardiac failure + diuretics

a reduced skin turgor. Capillary refill time was two seconds. Auscultation of the chest revealed a mild expiratory wheeze, and the remainder of the examination was unremarkable.

Preliminary blood tests revealed markedly low sodium at 102 mmol/L (normal range 135–145mmol/l). Potassium was also low at 3.2 mmol/L (normal range 3.5–5mmol/l). All other routine blood tests including a full blood count, renal and liver function tests and C-reactive protein were within normal range. An ECG, chest x-ray and urinalysis were also normal.

How can hyponatraemia present?

The clinical presentation of hyponatraemia is non-specific; malaise, lethargy, confusion, irritability, headache, nausea and anorexia may all be insidious presenting symptoms. Profound hyponatraemia may manifest with muscle cramps and neurological symptoms including weakness, convulsions, altered consciousness or even coma.^{2,5} Neurological effects are usually seen when sodium levels fall below 115 mmol/L and comprise a spectrum of symptoms under the umbrella term of 'hyponatraemic encephalopathy'.⁵ Cerebral oedema can result as water is drawn into brain cells along an osmotic gradient. The consequences of this can be devastating and may lead to tentorial herniation, brainstem impingement and death.^{5,6} The pace at which serum sodium concentration plummets also determines severity of illness. Sudden drops will result in an overwhelming fluid shift, causing severe neurological sequelae and a poorer prognosis. A steady decline, even to very low levels may be tolerated as neurones have sufficient time to acclimatise.⁵

Hyponatraemia may be diagnosed prior to referral to hospital, given the ease of access to blood testing in the community. In other cases the finding may not be apparent until after the patient's arrival on the AMU. The availability of near patient testing in most units will enable rapid identification of hyponatraemia. However, before embarking on further investigations and treatment, it is vital to ensure that the sample was not taken near the site of an existing hypotonic fluid infusion as this can result in an inaccurate measurement

of sodium concentration. It should also be remembered that hyponatraemia may be a consequence of a more significant chronic illness, such as cirrhosis or heart failure. Hyponatraemia has been shown to be a feature in up to 22% of cases of decompensated liver disease^{7,8} and in 27% of patients with heart failure.⁹

The history should include detailed enquiry into recent prescribed and non-prescribed medication, and recent diarrhoea or vomiting which may have led to dehydration, and any other symptoms of hypovolaemia. Symptoms or a past history suggestive of pulmonary, cranial, hepatic, renal or cardiac disease should also be sought, along with a careful smoking and alcohol history.

A past psychiatric history should alert suspicions of primary polydipsia (compulsive water drinking) as well as abuse of medications such as diuretics and antidepressant or antipsychotic drugs known to cause hyponatraemia.

What further investigation is required and how can biochemical abnormalities be interpreted?

Investigation into the cause of hyponatraemia with no apparent contributing illness requires evaluation of the patient's volume status, followed by measurement of urine and serum osmolalities and urinary sodium. Urine sodium is measured either over 24 hours or randomly, the former being of greater diagnostic value – although sometimes impractical.¹⁰ High urine sodium (above 30 mmol/L) sways the diagnosis towards SIADH, adrenal insufficiency (particularly if co-existing hyperkalaemia) or diuretic-induced hyponatraemia (Table 1). Renal pathology such as salt-wasting nephropathy and acute tubular necrosis, may also cause increased sodium excretion associated with hypovolaemic hyponatraemia. If this is suspected renal ultrasound scan should be considered. Low urine sodium (less than 20 mmol/L) is likely due to extrarenal losses including emesis, diarrhoea or cutaneous losses following burns or trauma. Nephrotic syndrome, liver

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Table 2. SIADH – diagnostic criteria¹⁰

Plasma sodium < 135 mmol/l
Urine osmolality >100 mOsm/kg
Urine sodium >30 mmol/l
Patient clinically euvolaemic
Exclusion of glucocorticoid deficiency
Hyponatraemia
Normal salt intake

cirrrosis and congestive cardiac failure can also cause decreased excretion of sodium.

Thyroid function tests should be requested as hypothyroidism can present with vague symptoms and hyponatraemia; in this case urinary sodium will be increased. Random serum cortisol or a short synacthen test must be undertaken to exclude adrenal insufficiency (Addison's), particularly in patients who have recently taken oral corticosteroids. Abnormalities in either of these endocrine axes are documented causes of low sodium.¹¹

Once the above conditions are excluded, a provisional diagnosis of SIADH can be made if the urine osmolality is >100 mOsm/kg.¹⁰ The essential diagnostic criteria for SIADH are shown in Table 2. Unfortunately, there is no reliable blood test for detecting elevated levels of ADH. Serum vasopressin is raised in more than 90% of cases of hyponatraemia, irrespective of aetiology.¹⁰ However, this assay is only available in certain centres and is not routinely used.

Other investigations should include a chest x-ray and measurement of serum calcium, which may be abnormal in patients with malignancy. A Computerised Tomography (CT) scan of the thorax/abdomen/pelvis may also be necessary if malignancy is considered likely.

Case vignette continued

Clinical assessment suggested that she was hypovolaemic; serum cortisol and thyroid function tests were unremarkable. Urine sodium came back as elevated (>30mmol/L) but serum osmolality was normal (285 mOsm/kg). A CT scan of chest, abdomen and pelvis was entirely normal. Urine was sent to the laboratory for a diuretic screen to rule out possible diuretic misuse.

How should a patient with hyponatraemia be managed?

In the acute setting, hypovolaemic hyponatraemia such as that seen in profuse diarrhoea or emesis is managed by replacing salt and water. Intravenous isotonic saline is the fluid of choice for restoring effective circulating volume. Hypertonic solutions are used when patients have severe neurological deficits as a result of hyponatraemia.

Compared to hypovolaemic hyponatraemia, the sodium balance in euvolaemic SIADH is normal as

it is not regulated by ADH but by aldosterone and atrial natriuretic peptide.¹² Administration of sodium, therefore, is likely to worsen hyponatraemia as water would be retained. Thus, treatment of euvolaemic hyponatraemia is centred around fluid restriction; the usual recommendation is between 0.8 to 1.2 litres over a 24 hour period.^{2,10} If fluid must be administered (e.g. in the case of neurological symptoms), serum sodium must be monitored and concurrent use of a loop diuretic may be useful in inducing ADH resistance and ultimately the production of dilute urine.¹²

Demeclocycline, a tetracycline antibiotic, is a typical pharmacological agent used in SIADH in patients who find fluid restriction difficult. It acts by opposing the effects of ADH, hence producing reversible nephrogenic diabetes insipidus. However, there is growing popularity for the use of vasopressin receptor antagonists (vaptans) in the management of euvolaemic and hypervolaemic hyponatraemic states. Vaptans induce aquaresis (i.e. excretion of water without electrolyte loss), thereby increasing serum sodium concentration. Their efficacy in treating acute hyponatraemia is now well accepted, although further studies are required to establish their role in the use of chronic hyponatraemia and their effect on morbidity and mortality. Vaptans are effective in the oral route, with the exception of conivaptan which has to be administered intravenously.¹³ Side effects include thirst, dry mouth and increased frequency of urination.¹⁴

Besides the use of vaptans, hypervolaemic hyponatraemia is managed with fluid restriction, as with euvolaemic causes. Sodium administration is generally contraindicated in hypervolaemic patients as this can exacerbate oedema.¹⁴

Central pontine myelinolysis (CPM) can occur when there is rapid elevation of plasma sodium concentration. In situations where saline is administered in the treatment of hyponatraemia, frequent measurement of serum sodium is recommended to ensure that the rate of rise of serum sodium does not exceed 12 mmol/L per 24 hours, or 8 mmol/L per 24 hours in alcoholics.^{2,10} CPM results from an inability of brain cells to adjust to dynamic changes in their surrounding medium. The subsequent fluid shifts are detrimental and may result in permanent brain damage.^{5,15} A similar process is involved when sodium concentration drops too quickly, as discussed earlier.

A note about iatrogenic hyponatraemia

It is imperative that a thorough medical history is elicited as numerous medications have been implicated as causes of hyponatraemia. Drugs most commonly reported to cause hyponatraemia include thiazide diuretics, sertraline and carbamazepine.^{17, 18} Table 3 shows the methods in which medications known

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to cause established hyponatraemia affect water and sodium haemostasis.

Case vignette continued

Sodium replacement with slow intravenous fluids (0.9% saline) was commenced. Once fluid had been administered and sodium levels had improved to 117 mmol/L, her volume status was reassessed. On day 3 of her admission, she was no longer deemed to be clinically dehydrated; skin turgor and renal function were consistent with a euvoelaemic state. The management then shifted to a fluid restriction regimen. On day 6, serum sodium had been corrected to 138 mmol/L.

The patient was discharged after steady clinical and biochemical improvement, with out-patient follow up arrangements in AMU clinic. At the time of discharge from hospital the cause of her hyponatraemia remained unclear, although results of her diuretic screen were not yet available. This subsequently confirmed the presence of furosemide in the urine, although the patient was not prescribed this drug and denied diuretic misuse. Careful enquiry at the time of follow-up in our AMU clinic revealed that the patient's daughter had been prescribed furosemide for the treatment of hypertension and it was considered likely that the patient had been deliberately, or inadvertently consuming these. Further support was sought via the community psychiatric team and the patient has since remained well.

Case conclusion

Diuretic misuse is most commonly seen in patients with anorexia nervosa and has been previously reported in the literature as a cause for hyponatraemia.¹⁶ Although our patient did not fit this typical pattern, suspicious were raised by the unusual combination of volume depletion combined with a raised urinary sodium, which was atypical for SIADH. Severe hyponatraemia is more commonly associated with use of thiazide

Table 3. Drugs commonly associated with hyponatraemia and their effect on water and sodium balance¹⁷

Effect on water +/- sodium haemostasis	Medication
Inhibits sodium chloride reabsorption in the distal tubules	Thiazide diuretics Thiazide-like diuretics
Inhibits sodium chloride reabsorption in the ascending loop of Henle	Loop diuretics
Produces exogenous ADH	Desmopressin Oxytocin
Increases hypothalamic production of ADH (SIADH)	Opioids ACE inhibitors PPI Amiodarone Theophylline Antidepressants (TCA, SSRI, MAOI) Haloperidol Anticonvulsants (carbamazepine, sodium valproate, leviteracetam)
Potentiates effects of ADH	Insulin Non-steroidal anti-inflammatory drugs Anticonvulsants (carbamazepine, lamotrigine)

ADH: antidiuretic hormone, MAOI: monoamine oxidase inhibitors, TCA: tricyclic antidepressants, SSRI: selective serotonin reuptake inhibitors

diuretics such as bendroflumethiazide,^{16,18} whereas in this case the loop diuretic furosemide was implicated. This highlights the importance of a systematic approach to the evaluation of patients with hyponatraemia and maintenance of an open mind with regard to more unusual causes when the pattern does not fit.

Conflict of interest

This study was funded entirely by the authors and they have no conflict of interest with any third party.

References

- Anderson RJ, Chung HM, Kluge R, *et al*; Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med*. 1985; 102(2):164–8.
- Mittal R, Shefiel H, Demssie Y; Management of hyponatraemia. *Br J Hosp Med (Lond)*. 2011; 72(2):22–5.
- Helwig FC, Schutz CB, Curry DE; Water intoxication. Report of a fatal case, with clinical, pathologic and experimental studies. *JAMA*. 1935; 104:1539–75.
- Arief AI. Hyponatremia, convulsions, respiratory arrest and permanent brain damage after elective surgery in healthy women. *N Engl J Med*. 1986; 314:1529–35.
- Moritz ML, Ayus JC; The pathophysiology and treatment of hyponatraemic encephalopathy: An update. *Nephrology Dialysis Transplantation*. 2003; 18 (12): 2486.
- Sterns RH, Nigwekar SU, Hix JK; The treatment of hyponatremia. *Semin Nephrol*. 2009; 29(3):282–99.
- Ginès P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. *Hepatology*. 2008; 48(3):1002–1010.
- Lindsay A. Profound hyponatraemia in cirrhosis: A Case Report. *Cases Journal* 2010; 3:77.
- Stephen RG. Hyponatremia and outcomes in patients with heart failure. *Heart*. 2012; 98:24 1761–62
- Thompson TJ, Crowley RK. Hyponatraemia. *J R Coll Physicians*. 2009 39:154–7
- Woo KH, Cho MH, Kim JK, *et al*. A Case of hyponatremia in hypothyroidism. *Korean J Nephrol*. 2007; 26(4):455–459.
- Sterns RH. Overview of the treatment of hyponatremia. In: UpToDate, Emmett, M (Ed), UpToDate, Rochester, USA. 2013.
- Narayan G, Mandal SN. Vasopressin receptor antagonists and their role in clinical medicine. *Indian J Endocrinol Metab*. 2012; 16:183–191.
- Schrier RW, Gross P, Gheorgiade M *et al*. Tolvaptan, a selective oral vasopressin V2- receptor antagonist for hyponatremia. *N Engl J Med*. 2006; 355:2099–112.
- Copeland PM. Diuretic abuse and central pontine myelinolysis. *Psychotherapy and Psychosomatics*. 1989; 52(1–3):101–5.
- Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatraemia, review and analysis of 129 reported patients. Clinical commentary. *Chest*. 1993; 103:601–06.
- Liamis G, Milonis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis*. 2008. 52:144–153.
- Fourlanos S, Greenberg P. Managing drug-induced hyponatraemia in adults. *Aust Prescr*. 2003. 26:114–7.