

Hyponatraemia in Hospitalised Adults: a Guide for the Junior Doctor

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Accepted: 8th December 2016

Provenance: externally peer-reviewed.

Abstract: Hyponatraemia is common and often a source of confusion for junior doctors. It is infrequently dangerous, but when it is, is a medical emergency and requires urgent treatment to avoid life-threatening cerebral oedema. Treatment of acute hyponatraemia is also potentially hazardous; it is therefore important to be able to recognise when urgent management is **not** indicated, and to investigate appropriately. This paper focuses on these issues, which are most likely to be the cause of consternation for the junior doctor. Recommendations are largely based on the 2014 joint European clinical practice guidance for management of hyponatraemia; the 2010 GAIN (N Ireland) guidance and 2013 American guidance are also referenced.

INTRODUCTION

Hyponatraemia is the most common electrolyte disorder encountered in clinical practice, occurring in up to 30% of hospital patients¹. It is seen in a wide variety of conditions and, in most situations is mild and simply a marker of disordered physiology².

Hyponatraemia is defined as a serum sodium < 135 mmol/L (laboratory reference range typically 135-145 mmol/L). It may be classified according to biochemical severity or to duration / time since onset²:

- Mild: 130-134 mmol/L
- Moderate: 125-129 mmol/L
- Severe: < 125 mmol/L
- Acute: < 48 hours duration
- Chronic: > 48 hours duration

Mild hyponatraemia is in itself not hazardous and any management should be that of the underlying disorder, where one is identified. More severe hyponatraemia, particularly when of rapid onset, may be associated with acute fluid shifts which can cause life-threatening cerebral oedema. This can be ameliorated with rapid infusion of hypertonic saline. However, inappropriate administration of hypertonic saline can itself have potentially very serious neurological consequences^{1,3}.

Thus it is very important to recognise when hyponatraemia is

a medical emergency needing urgent treatment before waiting for results of investigations, and when it is more appropriate to investigate first, which is by far the more common scenario. This may require rapid decision-making, particularly in hospital inpatients.

Hyponatraemia presents in many very different clinical situations; it is generally not well understood and is often poorly managed¹. In a recent audit of requests for advice from medical staff in Belfast Health & Social Care Trust Clinical Biochemistry department, 62% of all requests logged were in relation to abnormalities in serum sodium⁴. The potential consequences of both over- and under-treatment in the acute setting mean that all doctors looking after hospital inpatients must be able to investigate the cause and understand the results of investigations, be able to identify those at risk and treat patients appropriately and in a timely manner.

Both adults and children are at risk and indeed the relatively small skull:brain volume ratio found in children makes them more vulnerable to the effects of rapid fluid shifts⁵. The principles of investigation and management are the same; however, this article is focused on hyponatraemia in adults, and the rates and volumes of hypertonic saline suggested here do not apply to children (< age 16 years).

WHAT CAUSES HYPONATRAEMIA?

Hyponatraemia is very rarely due to sodium deficiency. The most important factor influencing the concentration of sodium in plasma (which is the intravascular component of extracellular fluid) is the relative amount of water in extracellular fluid. To understand what factors influence water balance and osmolality of plasma, it is necessary to first of all understand the underpinning physiology.

PHYSIOLOGY OF WATER BALANCE

Approximately 60% of an adult male's body mass is made up of water. Approximately 40% of total body water (TBW) is extracellular, the remaining 60% intracellular. Approximately 20% of extracellular fluid (ECF) is intravascular (ie plasma).

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Thus a 75kg man's body contains 45L of water, of which 18L is extracellular, and he has approximately 3.6L plasma. Adult females have proportionately more fat and are approximately 50% water. Equivalent calculations indicate that a 65kg woman has 2.6L plasma.

The extracellular and intracellular compartments are in osmotic equilibrium, and water moves freely across the cell membrane in response to changes in concentration of solutes present in serum or serum osmolality. Sodium is the most abundant solute in ECF, and is thus the largest contributor to serum osmolality. *Serum sodium concentration is essentially the ratio of amount of extracellular sodium to amount of extracellular water; the major determinant of serum osmolality, and serum sodium, is the amount of water in the ECF compartment.* The absolute amount of ECF sodium is much less commonly a factor.

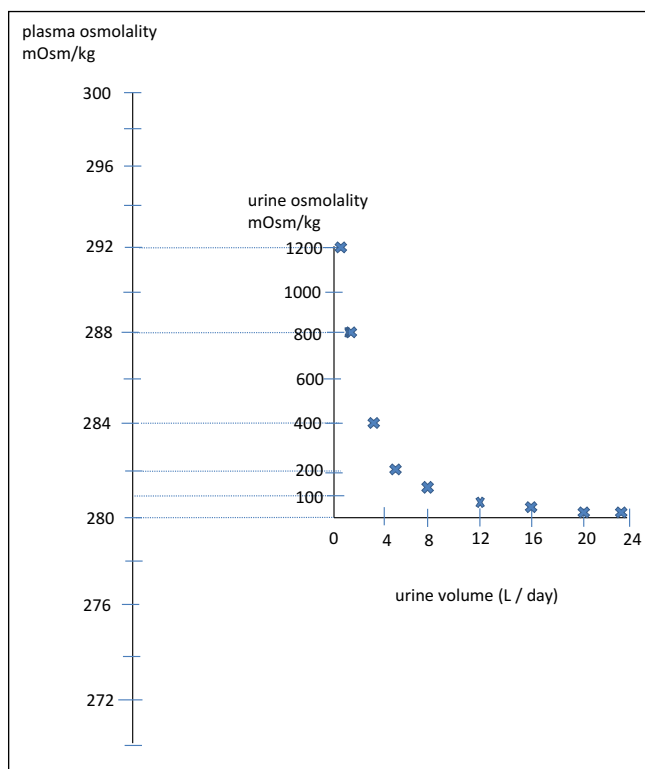


Fig 1. Normal physiological relationship between plasma osmolality, urine osmolality and urine volume in humans (taken from ref 1 Spasovski et al)

The main hormone that regulates extracellular water is anti-diuretic hormone (ADH), which is secreted by the posterior pituitary gland in response to high serum osmolality. It acts on the V2 receptors in the distal convoluted tubule and collecting duct of the kidney. This causes aquaporin 2 proteins to be inserted into the cell membrane, which increases its permeability to water. Water is drawn out of the collecting ducts, which makes the urine more concentrated (anti-diuresis), and into the blood, which decreases the serum osmolality and serum sodium concentration. ADH secretion is also a potent stimulator of thirst, which also brings more water into the ECF via fluid ingestion. Normal serum osmolality is 275-295 mOsm/kg. ADH switches on

at around 280 mOsm/kg, and the effect of this on urine osmolality can be seen in Fig. 1, which shows the relationship between plasma osmolality and urine osmolality and volume in healthy humans. There is clearly a much wider range of urine osmolality (< 100 to >1000 mOsm/kg) compared to serum osmolality, which is normally kept within a narrow range, primarily under the influence of ADH. It is apparent that, as plasma osmolality rises, urine becomes more concentrated and decreases in volume to conserve water. Thirst is stimulated at around 290mOsm/kg to bring more water into the system.

The renin-angiotensin-aldosterone system (RAAS) tightly controls excretion of sodium in the distal renal tubules, and also has an effect on serum sodium concentration via ADH release. Renin is released by the juxtaglomerular cells of the kidney in response to a low blood pressure and low circulating volume. This eventually leads to the conversion of angiotensin I to angiotensin II, which has two main functions in this context. Firstly, it stimulates the release of ADH, leading to increased water retention. It also causes aldosterone to be released, which leads to sodium (and therefore water) retention in the thick ascending loop of Henle.

Natriuretic peptides, particularly atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), also play a part in sodium regulation. Their main effect, in response to stretch of cardiac myocytes in the atria, is diuresis, ie sodium and water loss through the kidneys.

ABNORMAL WATER BALANCE LEADING TO HYPONATRAEMIA

Consideration of ECF volume or hydration state is useful in determining the cause, which frequently dictates the treatment.

1. *Decreased ECF volume* leads to ADH secretion via the RAAS, which acts to preserve intravascular volume. This may occur in salt-losing states such as excessive gastrointestinal losses, adrenal insufficiency or salt-losing nephropathies.
2. *Increased ECF volume* – cardiac failure, liver failure, renal failure and nephrotic syndrome are all associated with difficulty excreting water due to factors including decreased circulating blood volume, renal underperfusion and associated RAAS activation. Associated medication (notably diuretics) is a common complicating factor. Renal sodium loss will also be promoted by high concentrations of natriuretic peptides.
3. *Normal ECF volume* (euvolaemia) – hyponatraemia in this situation results from impaired excretion of water, usually due to inappropriate release of ADH. Syndrome of inappropriate antidiuresis (SIAD) occurs when ADH is secreted independently of serum osmolality or circulating volume. This leads to urine which is inappropriately concentrated and the failure to excrete water results in hyponatraemia. SIAD is essentially a

diagnosis of exclusion. True euvoelaemic hyponatraemia with inappropriately concentrated urine, in the absence of renal, adrenal or thyroid disease, or diuretic therapy, meets criteria for diagnosis of SIAD. SIAD occurs in a wide range of pulmonary, CNS and malignant conditions, as well as frequently being implicated in drug-induced hyponatraemia. It is a common cause of hyponatraemia but is probably overdiagnosed, frequently without other causes having been excluded³.

A further cause of euvoelaemic hyponatraemia is primary polydipsia – urine osmolality is very low indicating ADH suppression, but the water intake overwhelms the capacity to excrete water. This is particularly seen with concurrent low solute intake, eg anorexia nervosa, beer potomania and ‘tea and toast’ hyponatraemia – excretion of 1L of fluid requires co-excretion of 50-100 mmol of solute, e.g. urea, normally generated from dietary protein.

ASSESSMENT OF THE HYPONATRAEMIC PATIENT (Fig. 2)

How should I investigate a hyponatraemic patient?

The first question to ask is whether you have time to investigate fully, or whether you need to instigate urgent treatment, regardless of the cause, to prevent life-threatening cerebral oedema.

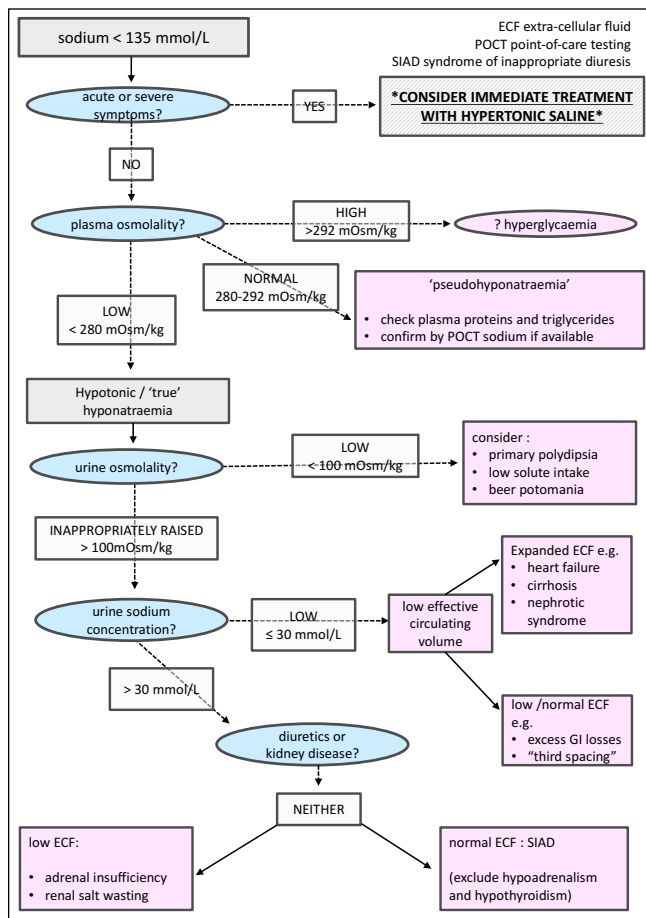


Fig 2. Algorithm for the investigation of hyponatraemia (adapted from Spasovski et al)

How do I decide who is at risk of cerebral oedema and needs urgent treatment?

The most pressing criterion to address is the presence or absence of symptoms which may herald incipient cerebral oedema. The joint European guidance on management of true hypotonic hyponatraemia emphasises the importance of managing the patient rather than the serum sodium concentration¹. The presence of any symptoms of cerebral oedema should be taken very seriously:

Box 1

Symptoms of cerebral oedema seen in symptomatic hyponatraemia¹

Severity Symptom	
Moderate	Headache
	Nausea
	Confusion
Severe	Vomiting
	Abnormal or deep somnolence
	Seizures
	Decreased level of consciousness
	Cardiorespiratory distress

It must be borne in mind that these symptoms are non-specific and may be the symptoms of the disorder causing the hyponatraemia. However if there is no apparent primary cause of such symptoms arising acutely in a patient with at least moderate hyponatraemia, and the hyponatraemia is not known to be chronic, urgent treatment with hypertonic saline is indicated.

Box 2

Some drugs and conditions associated with acute (< 48 hrs) hyponatraemia¹

- Post-operative phase (general anaesthesia)
- Post-resection of prostate or uterine surgery
- Polydipsia
- Prolonged exercise
- Recent thiazide prescription
- MDMA or Ecstasy ingestion
- IV cyclophosphamide
- Colonoscopy preparation

The 48 hours threshold arises from studies which indicate that the brain adapts to a chronic hyponatraemic state (>48 hrs) by extruding intracellular osmoles to maintain osmotic equilibrium, and so there is much less risk of cerebral oedema¹. Once the brain has adapted, brain cells are then vulnerable to the effects of increasing sodium too quickly, which can cause stripping of the neuronal myelin sheath leading to the potentially disastrous Osmotic Demyelination Syndrome (ODS). Patients at increased risk include those with malnutrition, hypokalaemia and a history of alcohol excess.



Thus the distinction between acute and chronic hyponatraemia is important. However duration is not always known, as quite frequently there has not been a recent measurement of sodium preceding the low one; if not known, and there is no clinical indication of a recent onset (most frequent causes - box 2), it may be safer to assume it is chronic, which is much more common, although clinical assessment should be undertaken to ensure there are no acute symptoms (see box 1).

If hypertonic saline is not indicated, the management of the hyponatraemia depends on the cause which, if possible, should be treated.

CLINICAL ASSESSMENT MAY REVEAL LIKELY CAUSES.

History: first ask about symptoms of acute hyponatraemia (headache, nausea). Then ask about symptoms of chest or CNS disease, or malignancy. Enquire about medical history (recent surgery; cardiac, liver or kidney disease), smoking and medication, especially those recently started. Ask about thirst and fluid intake.

Examination: assess volume status, looking for evidence of dehydration (reduced skin turgor, postural drop in BP, dry tongue) or oedema; however signs may be subtle⁶.

Laboratory assessment of serum and spot urine is the cornerstone of diagnosis and should be requested at an early stage in all patients with a moderate or severe hyponatraemia.

1. *Serum osmolality* is necessary to distinguish between true and pseudohyponatraemia. (Osmolality is measured in the laboratory, whereas calculated osmolality is based on certain assumptions which may be erroneous – lab measurement of serum osmolality should always be sought initially.) True hyponatraemia is associated with hypo-osmolar serum, i.e. < 275 mOsm/kg. If serum osmolality is normal, consider pseudohyponatraemia; this is a spuriously low sodium measurement seen in hyperproteinaemia or hypertriglyceridaemia when measured by an indirect ISE (Ion Selective Electrode) method. Measuring plasma protein and triglycerides, and/or measurement of sodium with direct ISE if available (most point-of-care assays) will provide confirmation of this. If serum osmolality is high, consider hyperglycaemia as a cause of hyponatraemia (glucose is an osmole and high levels will lead to ADH secretion and water retention).
2. In the presence of true (hypo-osmolar or hypotonic) hyponatraemia, *urine osmolality* distinguishes between excessive fluid intake (urine osmo < 100mOsm/kg) and failure to excrete water (urine osmo > 100 mOsm/kg).
3. If failure to excrete water, *urine sodium* distinguishes between low circulating blood volume (urine sodium < 30mmol/L) and SIAD (urine sodium > 30mmol/L). SIAD diagnosis also requires exclusion of cardiac, liver, renal, adrenal and thyroid disease, and diuretic therapy.

TREATMENT OF ACUTE SYMPTOMATIC HYPONATRAEMIA:

- **Prompt infusion of 200 mls 2.7% hypertonic sodium chloride solution over 30 min⁷**
- This is a medical emergency⁸ and senior assistance should be sought as soon as possible – advice is available at any time from a chemical pathologist, nephrologist, endocrinologist or ICU physician.
- Remeasure serum sodium 20 minutes after infusion ends.
- Repeat infusion of hypertonic saline may be necessary.
- Aim for a rise of 5 mmol/L, and not more than 10mmol/L, in the first 24 hours (maximum 8 mmol/L in those at risk of ODS).
- Determine the cause and remove or treat where possible.

TREATMENT OF CHRONIC ASYMPTOMATIC HYPONATRAEMIA

- Determine the cause and remove or treat where possible.
- Mild hyponatraemia may not require any treatment.
- Management of reduced circulating volume:
 - Restore ECF volume with intravenous 0.9% saline solution
- Management of expanded ECF volume:
 - Treat the cause
 - Fluid restriction
- Management of SIAD with moderate or severe hyponatraemia
 - First-line treatment is fluid restriction¹
 - Second-line treatment oral sodium chloride plus low dose loop diuretic (recommended by European guidance)¹
 - Demeclocycline is licensed in Europe for treatment of SIAD associated with malignancy and can be very useful in the short to medium term (it is not recommended in European guidance 2014¹, with low grade evidence; it is however recommended in US guidance 2013³). Follow-up monitoring is mandatory.

CASES

Q1. A 73 year old lady is admitted with hyponatraemia (sodium 114 mmol/L) and slightly low potassium of 3.2 mmol/L, found incidentally by her GP. When last checked 6 months previously, it had been 131 mmol/L. She has had no acute symptoms and examination is unremarkable. She had been recently started on citalopram by her GP and is also on metformin, ibuprofen and esomeprazole. On examination she is euvolaemic.



TABLE 1
Some causes of SIAD

Drugs	Pulmonary disease	CNS disease	Malignancy	Other
SSRIs	Bacterial pneumonia	Brain trauma	Carcinoma of :- bronchus	Pain
MAOIs	Viral pneumonia	Stroke	- endometrium	Nausea
Carbamazepine	Legionella pneumonia	Encephalitis	- oropharynx	General anaesthesia
Opiates	Aspergillosis	Meningitis	- stomach	Exercise
MDMA (Ecstasy)	Cystic fibrosis	Tumours	- duodenum,	
NSAIDs	Asthma	Subarachnoid haemorrhage	- pancreas	
Cyclophosphamide	TB	Subdural haematoma	- ureter	
Platinum compounds	Positive pressure mechanical ventilation	Cerebral aneurysm	- bladder	
Vinca alkaloids	Malignancy		- prostate	
Proton pump inhibitors				

(a) Would you give this lady hypertonic saline whilst awaiting further investigations?

(b) Her serum osmolality is 242 mOsm/kg; urine osmolality is 578 mOsm/kg; urinary sodium is 72 mmol/L. What is the most likely diagnosis? How do you manage her now?

A1. (a) No – treat the patient and not the lab result – this lady is not unwell and this is probably not an acute hyponatraemia. Hypokalaemia increases the risk of ODS with hypertonic saline.

(b) She has hypotonic hyponatraemia with an inappropriately concentrated urine. The high urine sodium implies that she is perfusing her kidneys. Clinically and biochemically this fits with SIAD, probably caused by the SSRI. Both NSAIDs and PPIs can also cause SIAD, though rarely¹.

Restrict fluid intake (e.g. to 800 mLs/day), monitoring fluid balance. Check thyroid and renal function and perform a short Synacthen test if indicated by the clinical context. Recheck serum sodium daily and urine sodium and osmolality after 2 days. If still SIAD picture, consider changing antidepressant.

Q2. A 34 year old lady is admitted with ‘thunderclap’ headache. Brain imaging confirms sub arachnoid haemorrhage. She is not on any medication. On admission examination is unremarkable; her serum sodium is 133 mmol/L. The following morning the nurses report that she is very sleepy and has been vomiting during the night. You find her difficult to rouse but neurological examination is otherwise normal and she is euvolaemic. Fluid balance is positive (intake > output) by 640 mls since admission 14 hours previously. U+E now shows serum sodium has fallen to 121 mmol/L.

(a) Would you give this lady hypertonic saline whilst awaiting further investigations?

(b) Her serum osmolality is 253 mOsm/kg; urine osmolality

is 925 mOsm/kg; urinary sodium is 37 mmol/L. What is the most likely diagnosis?

A2. (a) Yes. She has acute hyponatraemia, clinical history including a cause of SIAD, and most importantly, symptoms of moderate cerebral oedema. She should be given 150mls 2.7% sodium chloride solution over 20 min while you look for senior assistance.

(b) Investigations confirm hypotonic hyponatraemia with inappropriately very concentrated urine and urinary sodium is also consistent with SIAD. Need to exclude renal, thyroid and adrenal dysfunction.

Q3. A 39 year old man has had extensive small bowel resection for Crohn’s disease following which he has a persistently high intestinal output from his ileostomy. He is losing approximately 3 L / day and feels thirsty and weak. On examination he has sunken eyes, reduced skin turgor, blood pressure of 102/64 mmHg with a postural drop to 82/56 mmHg. His serum sodium is 125 mmol/L; urea is raised at 16mmol/L, creatinine also slightly raised at 141mmol/L. Previous serum sodium 1 week previously was 132 mmol/L, urea 9 mmol/L, creatinine 96 mmol/L.

(a) Would you give this man hypertonic saline whilst awaiting further investigations?

(b) Serum osmolality is 268 mmol/L; urine osmolality is 824 mOsm/kg; urine sodium is < 10 mmol/L. What is the most likely cause of his hyponatraemia? How would you treat him?

A3. (a) No. He is unwell, but the clinical picture is not of cerebral oedema and the hyponatraemia is not acute.

(b) Biochemistry is entirely consistent with the clinical picture of intravascular volume depletion due to sodium and water loss. He should be treated with infusion of resuscitation fluids such as 0.9% sodium chloride or Hartmann’s.



Q4. An 82 year old man is admitted for management of severe left ventricular dysfunction following acute myocardial infarction 6 weeks previously. On examination he has marked peripheral oedema and bibasal lung crepitations with a raised JVP. His blood pressure is 96/58mmHg. His serum sodium is 124 mmol/L.

- (a) What is the most likely cause of the hyponatraemia?
- (b) His serum osmolality is 262mOsm/kg; urine osmolality 642mOsm/L; urine sodium 44mmol/L. Does this alter your answer to (a)? What further information would you like to know? How do you manage him?

A4. (a) Pump failure leading to underperfusion of kidneys and failure to excrete water.

(b) No – although underperfusion of kidneys is associated with urine sodium < 30, he is likely to be on a diuretic which causes natriuresis. Medication history needs to be explored. Management is that of his left ventricular failure.

Q5. A 58 year old man was diagnosed with multiple myeloma and was admitted to start chemotherapy. He seemed well on admission; hydration was normal and he was not taking any medication. You were surprised to be told that his serum sodium was 124 mmol/L.

What is the most likely cause of his hyponatraemia?

- (b) His serum osmolality is 284 mOsm/kg; does this confirm your answer to (a)? Does he need urine investigations? What investigation do you request next?

A5. (a) Pseudohyponatraemia due to high plasma protein expanding the plasma volume and causing spurious hyponatraemia with indirect ISE measurement.

(b) Yes his serum osmolality is normal and he does not require investigation of his urine. To confirm, either total protein or, if available, POCT sodium measurement would be useful. POCT sodium usually employs different methodology and will indicate that the serum sodium is normal.

Q6 A 21 year old student with type 1 diabetes mellitus developed recurrent fainting episodes and was taken by ambulance to the Emergency Dept after one such episode at the end of the Christmas term. She denied any prescribed, over the counter or recreational drugs, but stated that she had been more prone to hypoglycaemia in recent months despite reducing her insulin doses. On examination she was neurologically intact. Her tongue was slightly dry and she had a postural drop in blood pressure but otherwise she appeared well. She was also noted to have an unusually tanned appearance for the season but had not been engaging in any artificial tanning behaviours or travel abroad.

Serum sodium was 119 mmol/L; potassium 5.4 mmol/L; urea 7.2 mmol/L; random blood glucose 3.2 mmol/L. tCO₂ 19mmol/L; chloride 95. Serum osmolality 250 mOsm/kg; urine osmolality 642 mOsm/kg; urine sodium 58 mmol/L

What is the diagnosis?

A6 Addison's disease or auto-immune primary adrenal insufficiency. More common in people with type 1 DM. Pigmented appearance classical and has been mistaken for 'fake tan'. Mineralocorticoid deficiency results in renal tubular loss of sodium causing mild intravascular volume depletion and in turn postural hypotension and fainting. Glucocorticoid insufficiency may reduce insulin requirements. Mild hyperkalaemia and normal anion gap metabolic acidosis are further biochemical effects of mineralocorticoid deficiency and yield further clues.

Q7 A 19 year old patient with a history of anorexia nervosa was admitted to a medical ward with a serum sodium of 115mol/L; urea 0.8 mmol/L, creatinine 36 mmol/L. She was underweight (BMI 17.6kg/m²) but appeared well; she was not clinically dehydrated and there was no oedema. BP 128/84. Lab investigation showed serum osmolality 228 mOsm/kg; urine osmolality 58 mOsm/kg.

What is the cause of the hyponatraemia?

A7 Polydipsia. Patients with eating disorders not infrequently water-load in order to suppress appetite or to falsify weight. The hypo-osmolar serum indicated that the hyponatraemia was not spurious. Urine was maximally dilute, appropriate to the very dilute serum. Urea and creatinine were low partly due to dilution, but also due to poor protein intake and low muscle mass. This patient admitted drinking 10-14 L of water or Coke Zero /day.

ACKNOWLEDGEMENT

The authors wish to thank Brona Roberts and Michael Fogarty for helpful comments on the draft manuscript.

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