Extreme hypernatraemia: a case report and brief review

Anthony D Holley, Stuart Green and Peter Davoren

Clinical record

A 44-year-old quantity surveyor was admitted to the emergency department after being found unconscious in his home. The night before, his child had noticed he was unable to communicate normally. On the day of admission, an ambient temperature of 42°C was recorded.

On presentation, the patient had a Glasgow Coma Scale score of 8/15 (E2, V2, M4), heart rate of 94 beats per minute, blood pressure of 80/54 mmHg, and temperature (tympanic) of 38.9°C. No meningism or rash were noted. He was profoundly dehydrated, with dry mucous membranes and decreased skin turgor. Neurological examination revealed bilaterally up-going plantar reflexes, normal tone and no localising features.

The patient had been unwell with nausea, headache and mild confusion for the 72 hours before admission. He had a history of an accidental gunshot wound to the head at the age of 18 years. Apart from mild, intermittently treated depression, he was well.

The patient was intubated, mechanically ventilated and given 1000 mL 0.9% NaCl intravenously. Non-contrast computed tomography showed a metallic foreign body centrally in the region of the third ventricle and bodies of the lateral ventricles, consistent with the history of a gunshot injury. While there was evidence of an old right frontal infarct, there was no intra- or extracerebral haemorrhage or mass effect (Figure 1).

Blood biochemical testing on admission revealed serum concentrations of sodium, 208 mmol/L (reference range [RR], 135–145 mmol/L); chloride, 168 mmol/L (RR, 100–110 mmol/L); potassium, 3.0 mmol/L (RR, 3.2–4.5 mmol/L); glucose, 7.0 mmol/L (RR, 3.0–7.8 mmol/L); urea, 26.7 mmol/L (RR, 3.0–8.0 mmol/L); creatinine, 0.35 mmol/L (RR, 0.50–1.0 mmol/L); and a calculated osmolality of 449 mOsm/kg (RR, 275–295 mOsm/kg). Sodium level was measured with a Roche modular Ion Selective Electrode (Hitachi Ltd, Tokyo, Japan), calibrated to a level of 180 mmol/L ($n = 20$) with a coefficient of variation of 1.2%. The profound hypernatraemia was confirmed with blood gas direct electrode analysis (Radiometer ABL610; Medical A/S, Copenhagen, Denmark), which has a documented coefficient of variance of 0.7 at 159 mmol/L. Coefficients of variance have not been determined at higher sodium concentrations for either method. Urine osmolality was 679 mOsm/kg with a urine sodium concentration of 79 mmol/L. Urine drug screen was negative. Full blood count was unremarkable.

ABSTRACT

A 44-year-old man presented with extreme hypernatraemia. The case is unique in three respects: the patient's plasma sodium concentration was 208 mmol/L; the aetiology was multifactorial, including essential hypernatraemia, hypodipsia and high ambient temperature; and the patient survived with full neurological recovery. We briefly review various disorders of thirst and osmorecepters.

Crit Care Resusc 2007; 9: 55–58

Figure 1. Computed tomography on admission
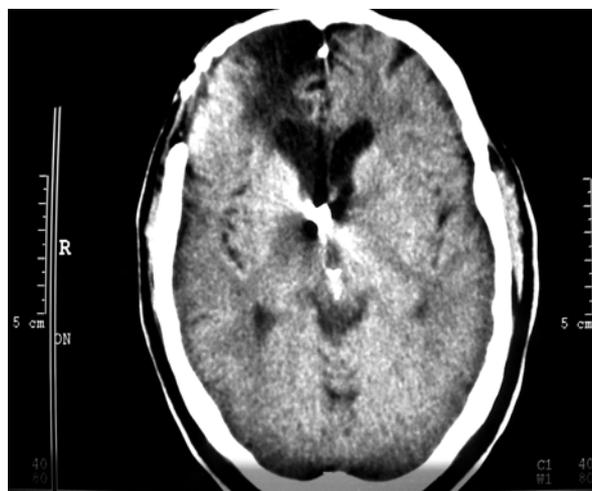
Computed tomography of the brain on admission showed a residual projectile fragment near the third ventricle and an old right frontal infarct but no intra- or extracerebral haemorrhage or mass effect.

Following intubation, arterial blood gas measurements were: pH, 7.28; $PaCO_2$, 48 mmHg; PaO_2, 124 mmHg; and HCO_3, 22 mmol/L. Cerebrospinal fluid examination revealed red blood cells, 2×10^6/L; white blood cells, 2×10^6/L; glucose, 5.4 mmol/L (RR, 2.8–4.0 mmol/L); protein, 2100 mg/L (RR, 150–500 mg/L); and negative Gram stain results.

The patient was managed for severe hypernatraemia, with resuscitation with 3000 mL isotonic saline initially, followed by 0.45% saline and 5% dextrose water. The water deficit was calculated to be 21.6 L given his documented weight of 87 kg. The patient's fluid balance over

Table 1. Patient's fluid balance over the 96 hours after admission

Day	In (mL)	Out (mL)	Balance (mL)
1	8 804	1 240	+ 7 564
2	6 836	3 305	+ 3 531
3	6 805	4 225	+ 2 580
4	8 090	2 468	+ 5 622
Total	30 535	11 238	+ 19 297

Figure 2. Patient's plasma sodium and urea concentrations over the 56 hours after admission
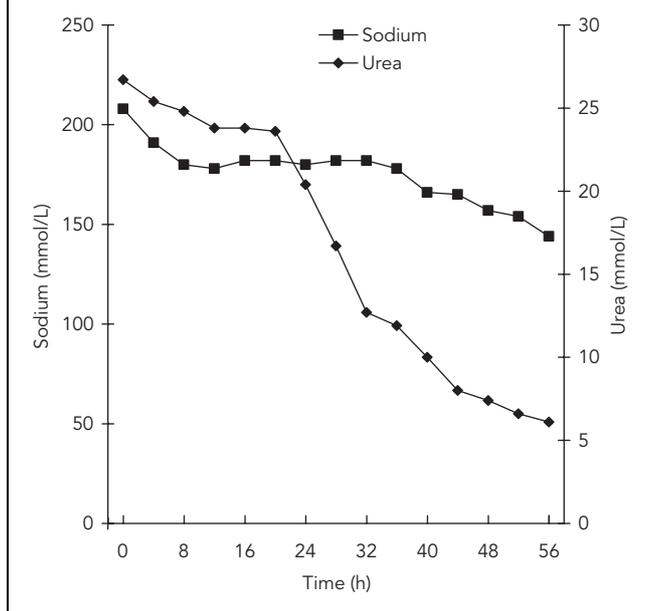
the first 96 hours is shown in Table 1. The probability that the hypernatraemia was acute on chronic mandated a gradual reduction in plasma sodium concentration. Plasma sodium concentration was initially measured 2- to 4-hourly to guide hypotonic fluid replacement (Figure 2).

By Day 5 of ICU admission, the patient was obeying complex commands and was successfully extubated. He was transferred to the medical ward under the care of an endocrinologist. On a water deprivation test, his peak serum osmolality was 325 mOsm/kg, with serum sodium concentration of 147 mmol/L, and urine osmolality of 743 mOsm/kg. He did not experience thirst during this test.

During his hospital stay, serum sodium concentration remained in the range 147–150 mmol/L without symptoms. The diagnoses were therefore essential hypernatraemia (also known as hypertonic reset osmostat syndrome), hypodipsia and possibly an element of partial central diabetes insipidus. The likely aetiology of these disorders

was hypothalamic injury secondary to the previous penetrating brain injury.

He made a full neurological recovery. Initial investigations of anterior pituitary function were inconclusive, but within 6 months of presentation the patient developed unequivocal hypopituitarism.

Discussion

Normal human cellular function depends on constant tonicity of the extracellular fluid. In health, water homoeostasis is so accurately controlled that plasma osmolality is precisely maintained within a remarkably narrow range of 275–298 mOsm/kg, and indeed within 1%–2% for a particular individual.[1]

The primary hormone that regulates plasma osmolality is arginine vasopressin (AVP), a nonapeptide, also known as antidiuretic hormone. It is produced by large neurones that originate in the supraoptic and paraventricular nuclei of the hypothalamus and project through the pituitary stalk to terminate on capillary plexuses scattered throughout the posterior pituitary. After synthesis in the cytosol of magnocellular neurones, the prepro-arginine-vasopressin-neurophysin II (prepro-AVP-NPII) precursor is translocated into the endoplasmic reticulum, where the signal peptide is removed, enabling the prohormone to fold and dimerise before transiting through the Golgi to the neurosecretory granules. At that location, it is further cleaved into the AVP, NPII and copeptin components and transported down the axon to be stored in nerve terminals until released by an excitatory stimulus.[2]

The regulation of AVP secretion is mediated by specialised cells, known as osmoreceptors, that are thought to be located in the anteromedial hypothalamus near the neurohypophyseal cell bodies in the supraoptic nucleus. These osmoreceptors are normally sensitive to small changes in effective osmotic pressure. A decrease in plasma osmolality of as little as 1%–2% rapidly suppresses AVP secretion to levels that permit a maximum water diuresis. Above this threshold, plasma AVP rises steeply in direct proportion to plasma osmolality and reaches a level sufficient to produce a maximum antidiuresis before plasma osmolality or serum sodium concentration exceed the normal range.[2] Nonosmotic variables can also influence AVP secretion. Reductions in blood volume or arterial pressure of more than 10%–20% stimulate AVP release, apparently by lowering the set point of the osmoregulatory system. These haemodynamic effects are mediated by neural pathways that originate in pressure-sensitive receptors in the walls of the left atrium and large arteries, and project via the vagal and glossopharyngeal nerves to the brain stem, from which postsynaptic pathways ascend to the hypothalamus. In

addition, AVP secretion is influenced by cortical input (pain, emotion and nausea), endocrine factors (thyroxine, corticosteroids and angiotensin II) and pharmacological influences (eg, fluoxetine, haloperidol and amphetamines).[1]

The effect of AVP in humans is to reduce the rate of urine flow by increasing the reabsorption of solute-free water from filtrate in the distal and collecting tubules of the kidneys. This effect is mediated via receptors, designated V2, that are located on the serosal surface of principal cells.[3] In the absence of AVP, the V2 receptors are inactive, and the cells lining the collecting ducts are impermeable to water.[4] When bound to AVP, the V2 receptors increase production of cyclic AMP, which increases the water permeability of the cell by perforating its luminal surface with preformed protein water channels known as aquaporin-2.[5] As a result of the increased permeability, most of the water in the diluted filtrate that reaches the distal nephron diffuses down the osmotic gradient created by the hypertonic milieu of the surrounding renal medulla. This increases the urine concentration and reduces urine flow by an amount proportional to the level of AVP. The ability of AVP to curtail water loss is restricted by a mandatory urine output required to excrete a given solute load. On a standard diet, this obligatory minimum is about 6–10 mL/kg/day. Extrarenal water loss approximates 10 mL/kg/day under basal sedentary conditions, but may increase several-fold during exposure to heat or physical activity.[6]

To prevent dehydration, some additional homoeostatic mechanism is necessary to ensure that irreducible renal and extrarenal water losses are appropriately replaced. This vital function is subserved by the thirst mechanism.

Thirst is regulated by hypothalamic osmoreceptors that are exquisitely sensitive to changes in the effective osmotic pressure of body fluids. It is thought that neural impulses from the osmoreceptors governing thirst sensation terminate in the cerebral cortex where they initiate drinking. The osmotic threshold at which thirst begins is about 5–10 mOsm/kg higher than the threshold for AVP release; therefore, overt thirst and polydipsia are not stimulated until an increase in sodium intake or water loss raises plasma osmolality by 1%–2%.[1]

Disturbances of the secretion or function of vasopressin, or of the regulation of thirst appreciation and drinking behaviour, can cause profound clinical abnormalities in sodium and water homoeostasis. A disruption in the water balance manifests as an abnormality in the serum sodium concentration — hypernatraemia or hyponatraemia. Hypernatraemia, defined as a rise in the serum sodium concentration to a value exceeding 145 mmol/L, is a common electrolyte disorder.[7] It is most frequently caused by excess water loss, and less frequently by increased sodium intake. Because sodium is a functionally impermea-

ble solute, it contributes to tonicity and induces the movement of water across cell membranes. Therefore, hypernatraemia invariably denotes hypertonic hyperosmolality and always causes cellular dehydration, at least transiently.[8] The resultant morbidity may be inconsequential, serious or even life-threatening. The mortality rate associated with hypernatraemia varies widely according to the severity of the condition and the rapidity of its onset. However, it is difficult to separate the contribution of hypernatraemia to mortality from the contribution of underlying illnesses.[9] Survival with severe hypernatraemia, defined as plasma sodium > 160 mmol/L, has frequently been described. However, only a few authors have described survival with extreme hypernatraemia (plasma sodium > 170 mmol/L).[10-16]

Our patient appeared to have a multifactorial aetiology for extreme hypernatraemia. The first component appeared to be a hypothalamic adipsic/hypodipsic syndrome. This condition results in defective osmoregulated thirst. It is frequently associated with defective osmoregulated AVP secretion and diabetes insipidus. Due to a lack of thirst sense, patients with this condition may fail to drink spontaneously and are at risk of hypernatraemia. This risk is increased if concurrent AVP insufficiency results in an inability to regulate free water clearance.[17] Disorders characterised by adipsia are uncommon, but a sufficiently large number have now been described for several distinct patterns of abnormal osmoregulation of thirst and vasopressin release to be recognised.

There are four main patterns of abnormal osmoregulatory function.[18] Type A adipsia is characterised by an upward resetting of the osmotic thresholds for both thirst and vasopressin release, and is sometimes referred to as essential hypernatraemia.[19,20] Welt proposed that the "chronic hypernatraemia syndrome" may result from the resetting of osmoreceptors around higher levels of plasma osmolality.[19] An osmoreceptor reset hypothesis predicts normal release of AVP when the new osmotic threshold is exceeded. However, some argue there is little evidence to support this concept.[21] Subsequent studies have shown that this abnormality could also result from partial or complete destruction of the osmoreceptors.

Type B adipsia is characterised by subnormal thirst and vasopressin responses to osmotic stimuli. The ability to secrete some AVP has led to the suggestion that type B adipsia is due to partial destruction of the osmoreceptors. Complete destruction of these receptors is classified as type C osmoreceptor dysfunction. Patients have complete absence of vasopressin release in response to rising plasma osmolality, and therefore present with adipsic diabetes insipidus, with lack of thirst despite marked polyuria. Finally, type D adipsia is an extremely rare form of osmoregulatory

dysfunction, manifesting as adipsia with intact osmoregulated AVP release.[18]

Our patient displayed features consistent with type A adipsia in association with chronic hypernatraemia. We propose that his previous penetrating brain injury is implicated in the osmoreceptor dysfunction and essential hypernatraemia. The subsequent development of pituitary dysfunction suggests that a new hypothalamic insult led to the presentation. The impaired urine-concentrating capacity also suggested an element of partial diabetes insipidus. An ischaemic event following his previous brain injury seems the likely explanation. We believe a third factor contributing to his profound hypernatraemia was the high ambient temperature at the time of presentation. This increased insensible water loss to a critical level, precipitating decompensation in an individual with an already compromised regulatory mechanism.

Our patient remains unique for the severity of his hypernatraemia and his survival without impairment. The case also illustrates the various osmotic regulatory mechanisms and their potential for malfunction.

Author details

Anthony D Holley, Senior Registrar,[1] currently Staff Intensivist[2]
Stuart Green, Senior Staff Intensivist[1]
Peter Davoren, Clinical Director, Diabetes and Endocrinology[3]

1 Department of Intensive Care Medicine, Gold Coast Hospital, Southport, QLD.

2 Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD.

3 Department of Medicine, Gold Coast Hospital, Southport, QLD.

Correspondence: Anthony_Holley@health.qld.gov.au

References

1 Black RM. Disorders of plasma sodium and plasma potassium. In: Irwin RS, Rippe JM, editors. Intensive care medicine. 5th ed. Philadelphia: Lippincott Williams and Wilkins, 2003: 864-76.

2 Robertson GL. Antidiuretic hormone normal and disordered function. *Endocrinol Metab Clin North Am* 2001; 30: 671-94.

3 Bichet D. Vasopressin receptors in health and disease. *Kidney Int* 1996; 49: 1706-11.

4 Douda TP, Valtin H. Cellular action of vasopressin in the mammalian kidney. *Kidney Int* 1976; 10: 46-63.

5 Knepper M. Molecular physiology of urinary concentrating mechanism: regulation of aquaporin water channels by vasopressin. *Am J Physiol* 1997; 272: F3-12.

6 Adolph EF. Physiology of man in the desert. New York: Hafner Publishing, 1969.

7 Adrogue HJ, Madias NE. Hypernatremia. *N Engl J Med* 2000; 20: 1493-9.

8 Kumar S, Berl T. Sodium. *Lancet* 1998; 352: 220-8.

9 Erasmus RT, Matusua TE. Frequency, aetiology and outcome of hypernatraemia in hospitalised patients in Umtata, Transkei, South Africa. *East Afr Med J* 1999; 76: 85-8.

10 Portel L, Hilbert G, Gruson D, et al. Survival with extreme hypernatraemia at 209 mmol/L. *Intensive Care Med* 1998; 24: 197-8.

11 Gomez-Daspet J, Elko L, Grebenev D, Vesely DL. Survival with serum sodium level of 180 mEq/L: permanent disorientation to place and time. *Am J Med Sci* 2002; 324: 321-5.

12 Park YJ, Kim YC, Kim MO, et al. Successful treatment in the patient with serum sodium level greater than 200 mEq/L. *J Korean Med Sci* 2000; 15: 701-3.

13 Sherer DM, Cutler J, Santoso P, et al. Severe hypernatremia after cesarean delivery secondary to transient diabetes insipidus of pregnancy. *Obstet Gynecol* 2003; 102: 1166-8.

14 Borrego DRR, Imaz RA, Lopez-Herce CJ, Serina RC. Severe hypernatremia: survival without neurologic sequelae. *Anales de Pediatria* 2003; 58: 376-80.

15 Addleman M, Pollard A, Grossman RF. Survival after severe hypernatremia due to salt ingestion by an adult. *Am J Med* 1985; 78: 176-8.

16 Goldszer RC, Coodley EL. Survival with severe hypernatremia. *Arch Intern Med* 1979; 139: 936-7.

17 Ball SG, Vaidja B, Baylis PH. Hypothalamic adipsic syndrome: diagnosis and management. *Clin Endocrinol (Oxf)* 1997; 47: 405-9.

18 McKenna K, Thompson C. Osmoregulation in clinical disorders of thirst appreciation. *Clin Endocrinol (Oxf)* 1998; 49: 139-52.

19 Welt LG. Hypo- and hypernatremia. *Ann Intern Med* 1962; 56: 161-4.

20 DeRubertis F, Michelis M, Davis B. Essential hypernatraemia. *Arch Intern Med* 1974; 134: 889.

21 Oh M, Carroll H. Essential hypernatremia: is there such a thing? *Nephron* 1994; 67: 144-5. ❑