

Adipsic hypernatremia with a reset osmostat

*Bhasker Bappal, FRCP (Glasg), FRCPCH (UK),
Hala A. Sheikh, MD, FRCPCH (UK),
Ajitha Radhakrishnan, MD, MRCP (UK),
Waad-Allah S. Mula-Abed, MSc, FRCPATH (UK).*

Despite the wide variation in the daily intake of sodium and water, plasma osmolality and sodium are maintained within normal range by vasopressin [arginine vasopressin (AVP) or antidiuretic hormone (ADH)] secretion and thirst. The osmotic threshold for AVP secretion is 283 mOsm/kg and for thirst sense is 293 mOsm/kg. Hence, by the time plasma osmolality reaches the osmotic threshold for thirst, AVP secretion would achieve maximum urine concentration.¹ In normal individuals, if water intake is voluntarily increased, the resultant fall in plasma osmolality will cut off AVP secretion allowing excess water to be excreted in urine, thereby maintaining normal plasma osmolality. If the sense of thirst is intact, patients with central diabetes insipidus can almost completely manage to maintain plasma osmolality near normal by increasing water intake. However, if the sense of thirst is lost (adipsia), the intact osmoregulated AVP secretion by itself cannot compensate even at its maximum response as it cannot stimulate water intake.¹

A 10-year-old boy, previously healthy, presented to the Pediatric Outpatient Department at the Royal Hospital, Muscat, Sultanate of Oman, with a 3 months history of intermittent headache, lethargy and general weakness with hypernatremia (sodium 178 mmol/L) as an incidental finding. There was no vomiting, visual disturbances, polyuria, polyphagia, excessive thirst or any history of central nervous system infection or head trauma. General examination did not reveal any abnormality. He was prepubertal with height of 148 cm (>97 percentile) and weight 37 kg (>90 percentile). His blood pressure and temperature were normal, and pulse rate was 100/min. There was no clinical evidence of dehydration and skin was not doughy. His visual fields and ocular fundi were normal. The rest of the systemic examination was unremarkable. During his hospital stay, no behavioral, emotional or sleep disturbances were observed.

The results of the following investigations were normal: complete blood count, liver function tests, serum calcium, phosphate, alkaline phosphatase and uric acid. Serum electrolytes were: sodium 178 mmol/L, potassium 4.4 mmol/L, chloride 155 mmol/L, urea

8.9 mmol/L and creatinine 90 µmol/L. The report of arterial blood gases was: pH 7.23, pCO₂ 5.87 kpa, HCO₃ 18 mmol/L, base excess -9.6 mmol/L and oxygen saturation 96.1%. The data collected while he was undergoing management for hypernatremia are listed in **Table 1**. Further, investigations revealed normal values for serum free thyroxin, thyrotropin, follicle-stimulating hormone, luteinizing hormone, prolactin, cortisol, β-human chorionic gonadotrophin and alpha-fetoprotein. His skeletal age was assessed as 10 years. Ultrasound examination of the kidneys revealed no abnormality. EEG was normal and the MRI of the brain did not show any hypothalamic or pituitary lesion.

When the patient was left to his own, he was comfortable on a low fluid intake. It was conspicuous that he never felt the desire to drink water despite severe hypernatremia (**Figure 1**). In the basal state, his fluid intake and urine output were closely matched. The urine output was only 500 ml/24 hours (0.6 ml/kg/hr), being the minimum obligatory urine output. Following free water replacement, his plasma osmolality and serum sodium failed to normalize. Instead of retaining water there was diuresis and urine output almost matched water intake. As sufficient amount of free water failed to correct the plasma osmolality and hypernatremia, replacement therapy with intranasal desmopressin [1-deamino-8-D-arginine vasopressin, (DDAVP)] was added and increased gradually to 10 microgram twice a day (**Table 1**).

On discharge, the parents were advised to monitor his weight, and maintain a strict fluid intake-output chart daily. The amount of free water intake advised during home management was 2.0-2.5 litres/day. Ensuring a urine output of 1000-1200 ml/day was considered to be a good indirect indicator for near normal plasma osmolality and, adequate water intake and DDAVP replacement. Similarly, rapid weight loss and decrease in urine output was presumed to indicate reduced water intake or poor compliance. Serum sodium was monitored weekly first and then fortnightly. During the first few months, the above obligatory water intake was effective. With passage of time, the initial enthusiasm and co-operation shown by the patient to drink a fixed quantity of water gradually waned. In the latter part of the first year, the patient presented again with an intense headache due to severe hypernatremia (sodium 176 mmol/L) mainly due to the lack of adherence to fixed water intake for nearly 2 weeks. On yet another occasion, he developed cerebral edema due to the inadvertent rapid oral rehydration to correct the hypernatremia. He developed generalized seizures and was ventilated.

Clinical Notes

Table 1 - Serum sodium, plasma, and urine osmolality during free and obligatory water intake and after DDAVP administration.

Day	Water intake	Intake/Output (ml/day)	Weight (kg)	Serum sodium (mmol/L)	Plasma osmolality (mOsm/kg)	Urine osmolality (mOsm/kg)	Serum AVP (pg/ml)	Nasal DDAVP (μ g/day)
1	F	600 - 500	37	176	358	1062	5.8	
3	O	1850 - 1400		166	336	673	1.5	
5	O	2050 - 2370		158	335	572		
7	O	2075 - 2240		157	325	456	< 1	
11	O	2270 - 1000	38	143	292	622		10
15	O	1625 - 1150	39	142	297	886		10
21	O	1050 - 800	40	137	288	996		20

DDAVP - 1-deamino-8-D-arginine vasopressin (Desmopressin), F - Free, O - Obligatory (predetermined water intake), AVP - arginine vasopressin

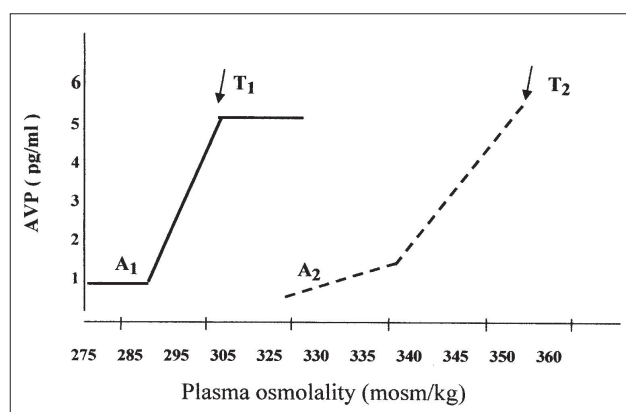


Figure 1 - Normal (—) and shift of osmotic threshold for arginine vasopressin (AVP) and thirst to right (---). T₁ - Normal threshold for thirst, T₂ - Shift to right without thirst, A₁ - Normal osmotic threshold, and A₂ - Patient's reset osmostat for AVP release.

However, he promptly recovered without any residual neurological problems. The EEG and MRI of the brain did not show any abnormality. The follow up during the subsequent 2 years has been very irregular; however, he has generally remained asymptomatic. Serum sodium ranged from 155-170 mmol/L depending on the degree of compliance. His growth, onset and progression of puberty were normal. No new abnormalities in the hypothalamic-pituitary function were identified during his follow up.

In this reported case, plasma osmolality (358 mOsm/kg) at presentation was life threateningly high with only few non-specific clinical symptoms. The boy denied any sense of thirst and gained 3 kg weight following rehydration in 21 days. The patient had free access to water and, therefore, the presence

of hypernatremia without associated polydipsia and polyuria clearly suggests adipsia. At the time of admission, serum sodium was 178 mmol/L, plasma osmolality was 358, and urine osmolality was 1062 mOsm/kg with the corresponding peak AVP was 5.8 pg/ml. Normally, at plasma osmolality of approximately 295 mOsm/kg, the mean plasma AVP usually reaches or exceeds 5 pg/ml, and this is sufficient to produce maximal urine concentration.² The AVP concentration observed at peak plasma osmolality was comparable to its concentration in normal individuals.² However, in a patient whose osmostat is reset at a higher level, AVP concentration may reach even higher value with raising plasma osmolality. Unfortunately, it was unethical to test this hypothesis by increasing the plasma osmolality further by water restriction or by saline infusion. When the water intake was increased, plasma osmolality declined marginally from 358-336 and then to 325 mOsm/kg. The corresponding fall in urine osmolality was more impressive as it decreased from 1062-673 mOsm/kg and then to 456 mOsm/kg. This disproportionate drop in urine osmolality was not matched by concurrent fall in plasma osmolality. The reduction in plasma AVP concentration from 5.8-1.5 and then to <1 pg/ml was more dramatic than the fall in urine osmolality, indicating increased sensitivity of the renal tubules to AVP, a phenomenon that has been reported in adipsia.³ In the reported patient, there was also a shift in the osmotic threshold for AVP release as there was a rightward shift to 325 mOsm/kg, with a peak response at 358 mOsm/kg. As there was no polyuric phase in the clinical course of the patient, it could be inferred that adipsia started first. Also, as the patient was totally devoid of thirst even in the presence of hyperosmolality, it could be assumed that the thirst center was completely damaged in

this patient. Further, it could be hypothesized that chronic hypernatremia itself might have resulted in a shift of the osmostat center for AVP release to the right resulting in relative deficiency of AVP. Adipsic hypernatremia with normal setting of osmostat has also been described with no demonstrated structural lesion.⁴

Cerebral edema is a well-known complication in adipsic patients particularly when rapid correction of hypernatremia is attempted, as in the case reported. This is more likely to occur in adipsic patients who are unable to dilute urine maximally due to fixed or erratic secretion of AVP irrespective of plasma osmolality.⁵ In the patient described, the cause of cerebral edema was attributable to the rapid water loading compounded by DDAVP.

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From the Department of Child Health (Bappal, Sheikh, Radhakrishnan) and the Department of Chemical Pathology (Mula-Abed), Royal Hospital, Muscat, Sultanate of Oman. Address correspondence and reprint requests to: Dr. Bhasker Bappal, Department of Child Health Endocrine and Metabolic Unit, Royal Hospital, PO Box 1331, Seeb 111, Muscat, Sultanate of Oman. Fax: +968 (2) 4599410. E-mail: bappal@omantel.net.om

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