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Hypernatraemia and polyuria in a patient with acute myeloid leukaemia and allogeneic bone marrow transplant

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Case Report

A 36-year-old man was admitted to our hospital with a history of weight loss of 5 kg and pancytopenia with 74% myeloid cells. His past medical history included tonsillectomy during childhood, concussion in 1985 and several minor sport injuries. A diagnosis of acute myeloid leukaemia (type FAB M2) was confirmed by bone marrow examination.

The first cycle of chemotherapy consisted of cytarabin and idarubicin (16.07.96 to 23.07.96), followed by cytarabin and amsacrin (17.08.96 to 22.08.96). The follow-up bone marrow examination showed aplasia without any leukaemic cells. As a result bone marrow transplantation was planned. After whole-body irradiation and conditioning therapy with etoposide and cyclophosphamide, allogeneic bone marrow transplantation was performed on 17.10.96, using an HLA-identical brother as the donor. Immunosuppressive therapy with cyclosporin A and methotrexate was started. A few days post-transplantation pneumonia developed and respiratory tract obstruction secondary to severe mucositis. Blood cultures were positive for oxacillin-resistant coagulase-negative staphylococci. In spite of antibiotic therapy with vancomycin the patient's condition deteriorated and he required intubation (28.10.96).

During the second week after transplantation the patient developed progressive hypernatraemia and rapidly rising blood urea concentration, combined with a minor increase in plasma creatinine. The patient remained haemodynamically stable, requiring no vasoactive drugs. Massive polyuria (up to 7 litres a day) developed, without administration of diuretic drugs. The patient received intravenous isotonic saline and 5% glucose solution. The central venous pressure remained within the normal range. Before intubation on 28.10.96 the patient had received parenteral nutrition with 2400 kcal per day. Thereafter nutrition was limited to the glucose in the infusion fluid (up to 300 kcal per day). The patient was sedated with midazolam and fentanyl and antibiotic therapy included vancomycin, imipenem–cilastatin, piperacillin, and ciprofloxacin. Prophylactic antiviral therapy with acyclovir had been started at the time of transplantation and was continued. On 2.11.96, with a plasma sodium concentration of 162 mmol/l, the patient developed myoclonus of the right leg and pupillary asymmetry. A CT scan of the brain showed mild subarachnoid haemorrhage around the left anterior and occipital lobe and in the right sylvic fissure. Tables 1 and 2 summarize important clinical and laboratory findings during the development of hypernatraemia.

Pathophysiology of hypernatraemia

Sodium is the effective osmole in the extracellular compartment. It is regulated within narrow limits

Table 1. Laboratory findings

Date	Plasma creatinine (μmol/l)	Plasma urea (mmol/l)	Plasma sodium (mmol/l)	Plasma osmolality (mOsmol/kg)	Urine osmolality (mOsmol/kg)
24 Oct	87	10.6	135		
25 Oct	95	14.1	136		
26 Oct	97	17.4	139		
27 Oct	97	18.8	145		
28 Oct	109	21	152	334	360
29 Oct	136	23.6	148		
30 Oct	148	26.1	152		
31 Oct	138	26.8	155	341	387
1 Nov	141	34.5	156	428	
2 Nov	132	36.5	162		
3 Nov	110	32.3	162	367	512
4 Nov	110	27.1	156	344	489
5 Nov	87	22	144	317	461
6 Nov	87	23.6	149	321	492
7 Nov	85	19.6	145	314	464
8 Nov			143		

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Table 2. Clinical findings during the development of hypernatraemia

	27 Oct	28 Oct	29 Oct	30 Oct	31 Oct	1 Nov	2 Nov
Central venous pressure (mmHG)	∅	13	7–16	10–16	12–18	12–16	9–17
Temperature (°C) daily maximum	39.4	38.4	38	37.2	37.4	37.7	37.3
Volume infused (ml per day)	5650	∅	6198	8240	5164	5861	5328
Urine volume (ml per day)	6100	∅	5195	7350	4835	6610	7205

∅ Not measured.

(137–141 mmol/l). The increase in plasma osmolality, induced by a rising plasma sodium concentration results in water movement out of the cells into the extracellular fluid and the resultant cellular dehydration of brain cells is responsible for the dominant neurological symptoms (lethargy, seizures, coma). The decrease in brain volume can cause rupture of cerebral veins, resulting in intracerebral or subarachnoid haemorrhage [1,2]. This did occur in our patient and may have been precipitated by thrombocytopenia after the bone marrow transplantation. The severity of hypernatraemic neurological symptoms is related primarily to the rate of rise in plasma osmolality rather than to the absolute degree of hypernatraemia. Thus patients with chronic stable hypernatraemia can be asymptomatic [3].

Hypernatraemia is induced either by negative water balance or by sodium overloading. Normally, whenever plasma sodium concentration increases, thirst develops and antidiuretic hormone is secreted. If the patient is conscious and has free access to drinking water, hypernatraemia will not develop. However, thirst and ingestion of water may not be provoked in severely ill patients because of altered mental state, weakness or mechanical ventilation. Table 3 summarizes the different aetiologies of hypernatraemia.

Table 3. Aetiology of hypernatraemia [7]

Water loss
1. Insensible loss
   sweating, fever
   burns
   respiratory infections
2. Gastrointestinal loss
   Osmotic diarrhoea
3. Renal loss
   Central diabetes insipidus
   Acquired disorder of urine concentration ('renal diabetes insipidus')
   Osmotic diuresis
4. Hypothalamic disorders
5. Water loss into cells (by increase of intracellular osmolality)
   Seizures
   Lactic acidosis
   Rhabdomyolysis

Sodium retention
Administration of hypertonic NaCl or $NaHCO_3$
Oral salt overloading

Aetiology of hypernatraemia in the above case

No hypertonic NaCl or $NaHCO_3$ infusions were given and accidental Na^+ overload could thus be excluded. Plasma lactate and creatine kinase levels repeatedly determined during the course of the illness were within the normal range, which excluded water loss into the intracellular space as a result of lactic acidosis or rhabdomyolysis. Gastrointestinal water loss by diarrhoea was not observed. In spite of hypernatraemia heart rate, blood pressure and central venous pressure remained within normal limits. Thus hypovolaemia due to dehydration was not readily apparent. However, the rising plasma creatinine concentration (maximal plasma creatinine 148 μmol/l) pointed to a decreasing glomerular filtration rate, which was presumably provoked by borderline hypovolaemia despite generous fluid replacement with isotonic saline and glucose infusions (see Table 2).

In spite of rising plasma Na^+ levels polyuria persisted (Tables 1, 2). Thus hypernatraemia had to be caused by renal water loss in the face of either undisturbed or defective urinary concentrating ability (Table 4).

Polyuria and hypernatraemia induced by central or renal diabetes insipidus can be distinguished from the consequences of solute diuresis with intact urinary concentration by measuring the urine osmolality and by calculating free water clearance. Osmotic diuresis is likely when daily solute excretion exceeds 1400 mosmol (or >20 mosmol/kg body weight/day) [4], as observed in our patient (e.g. on 1.11.96, 2829 mosmol/day). A hyp-

Table 4. Aetiology of hypernatraemia combined with polyuria (adapted from [4])

Water diuresis (impaired urine concentration):
  Urine osmolality <250 mosmol/kg
    Central diabetes insipidus
    Renal disturbance of urine concentration
    ('renal diabetes insipidus')
Solute diuresis:
  Urine osmolality >300 mosmol/kg
    Saline loading
    Hyperglycaemia
    Mannitol therapy
    Urea-induced osmotic diuresis
    Na^+ wasting nephropathy

Table 5. Urea excretion and calculated protein catabolism

	21 Oct	25 Oct	2 Nov
Plasma sodium (mmol/l)	133	136	162
Urea excretion/24 h (mmol/24 h)	365	709	2174
Protein catabolism (g/24 h)*	63.8	124.0	380.4

*Protein catabolism/24 h (g) = urea (mmol/24 h) × 0.175.

erosmotic urine as measured repeatedly in our patient (Table 1) is indicative of solute diuresis. Furthermore central diabetes insipidus was unlikely because desmopressin failed to raise urine osmolality. Diminished urine concentrating ability would lead to free-water excretion or an appreciably positive free-water clearance (C_{H_2O}) [4]. Free-water clearance in our patient, however, was negative, indicating free-water reabsorption by a concentrating kidney (data obtained on 31.10.96):

$$C_{H_2O} = \text{urine vol} \times \left[1 - \frac{\text{urine osm}}{\text{plasma osm}}\right]$$
$$= 4835 \times \left[1 - \frac{387}{341}\right] = 652 \text{ ml/24 h}$$

This amount of free water reabsorbed, though relatively small, is well within the normal urinary concentrating capacity in view of reduced renal perfusion with decreased glomerular filtration rate due to dehydration.

The most common causes of polyuria due to solute diuresis are uncontrolled diabetes mellitus with glucosuria and infusions with hypertonic mannitol, which both were absent in our patient. Another possibility is urea induced osmotic diuresis as observed following high-protein tube feedings [5], or urea administration to correct hyponatraemia in the syndrome of inappropriate ADH secretion [6]. In fact our patient's blood urea concentration rose quite excessively from 10 mmol/l (24.10.96) to 36 mmol/l (2.11.96) and so did urea excretion, which peaked at over 2000 mmol/24 h on 2.11.96 (Table 5).

Where did all this urea come from? From the case history we know that parenteral nutrition was discontinued for unclear reasons when the plasma sodium concentration started to rise. Massive catabolism of body proteins due to severe illness and inadequate caloric supply must have led to the endogenous production and urinary excretion of large quantities of urea which occurred simultaneously with the development of hypernatraemia. The amount of free water needed to excrete this tremendous urea load can be estimated indirectly by calculating the electrolyte free water reabsorption $T^e_{CH_2O}$ [4]. Our patient's calculated $T^e_{CH_2O}$ on 01.11.96:

$$T^e_{CH_2O} = \text{urine vol} \times \left[\frac{U_{NA} + U_K}{P_{NA}} - 1\right]$$
$$= 6661 \times \left[\frac{35 + 41}{156} - 1\right] = -3415 \text{ ml/24 h}$$

The negative value indicates that on this day 3.4 litres of normally reabsorbed free water were lost by 'non-electrolyte' solute diuresis.The cause of hypernatraemia becomes apparent: free-water loss by urea osmotic diuresis. The excretion of large amounts of urea induced by severe metabolic stress with high protein turnover required large urine volumes. The free-water loss led to hypernatraemia. Because of mechanical ventilation and sedation the patient was incapable of correcting his water deficit by drinking.

Diagnosis

1. Life-threatening hypernatraemia induced by urea osmotic diuresis;
2. Hypernatraemia-induced subarachnoid haemorrhage.

Conclusion

Differential diagnosis of hypernatraemia in severely ill patients with metabolic stress should include osmotic urea diuresis. Treatment requires administration of adequate amounts of electrolyte-free glucose solution to supply sufficient water and calories.

Follow up

After correction of free-water depletion with isotonic glucose infusion and starting adequate parenteral nutrition, plasma sodium concentration normalized (see Table 2). The patient left the hospital in good condition without any neurological deficit despite the subarachnoid haemorrhage.

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